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Gestational Diabetes Mellitus Changes the Metabolomes of Human Colostrum, Transition Milk and Mature Milk

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Background: Gestational diabetes mellitus (GDM) is a pregnancy complication that is diagnosed by the novel onset of abnormal glucose intolerance. Our study aimed to investigate the changes in human breast milk metabolome over the first month of lactation and how GDM affects milk metabolome.

Material/Methods: Colostrum, transition milk, and mature milk samples from women with normal uncomplicated pregnancies (n=94) and women with GDM-complicated pregnancies (n=90) were subjected to metabolomic profiling by the use of gas chromatography-mass spectrometry (GC-MS).

Results: For the uncomplicated pregnancies, there were 59 metabolites that significantly differed among colostrum, transition milk, and mature milk samples, while 58 metabolites differed in colostrum, transition milk, and mature milk samples from the GDM pregnancies. There were 28 metabolites that were found to be significantly different between women with normal pregnancies and women with GDM pregnancies among colostrum, transition milk, and mature milk samples.

Conclusions: The metabolic profile of human milk is dynamic throughout the first months of lactation. High levels of amino acids in colostrum and high levels of saturated fatty acids and unsaturated fatty acids in mature milk, which may be critical for neonatal development in the first month of life, were features of both normal and GDM pregnancies.

MeSH Keywords: Diabetes, Gestational • Metabolome • Milk, Human

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Background

Gestational diabetes mellitus (GDM) is defined as hyperglycemia that is first diagnosed during mid-pregnancy and its prevalence ranges from 9.3% to 25.5% worldwide [1]. Pregnant women with uncontrolled hyperglycemia have higher incidences of complications for both the mother and the fetus [2,3], such as fetal growth restriction (FGR), embryonic death, fetal malformation, and postpartum type-2 diabetes [4,5]. Although breastfeeding has been assumed to be an important low-cost intervention for women with GDM, and women with GDM are encouraged to breastfeed their babies at least for 3 months [6], it remains to be determined whether GDM affects the composition of breast milk during lactation.

Breast milk is produced by the mammary glands [7], and it is composed of fatty acids, proteins, sugars, immune cells, and bioactive molecules, which help immune system and organ development during a child's first 6 months of life [8]. The composition of breast milk varies throughout the lactation period; therefore, breast milk is also called colostrum, transition milk, and mature milk in terms of the different stages of lactation. Colostrum is produced until the 5th day of lactation, transition milk is produced until the 14th day; and mature milk is synthesized beginning at the end of the 2nd week of lactation [9]. Breast milk composition can be affected by maternal age, weight, diet, and health condition [10,11], but how GDM influences breast milk content is still unclear.

Metabolomic profiling involves the systematic study of low-molecular-weight (<1 kDa) endogenous and exogenous metabolites (e.g., lipids, amino acids, and organic acids) that represent cellular functions at the intersection of genetic and environmental effects [12,13]. Metabolomic analyses have recently been considered promising tools to study milk nutritional quality [14]. In the present study, we performed gas chromatography-mass spectrometry (GC-MS) to determine the metabolites in breast milk; this may aid in an in-depth understanding of the components and variations in breast milk between women with GDM and women with uncomplicated pregnancies.

Material and Methods

Study population

A total of 100 pregnant women with GDM and 100 women with uncomplicated pregnancies who were seen at the Department of Obstetrics of The First Affiliated Hospital of Chongqing Medical University (Chongqing, China) from January 2016 to December 2016 were randomly recruited (registration number: chiCTR-ROC-17011508). The diagnosis of GDM was defined according to the International Association of Diabetes and Pregnancy (IADPSG) guidelines with a 75 g oral glucose tolerance test (OGTT) that resulted in fasting glucose ≥5.1 mmol/L, 1-hour glucose ≥10 mmol/L, or 2-hour glucose ≥8.5 mmol/L. Individuals with pregestational diabetes mellitus or other major pregnancy complications, such as preeclampsia, intrahepatic cholestasis, etc., were excluded. Due to loss of follow-up, complete sampling of colostrum, transition milk, and mature milk was achieved for 90 women with GDM and 94 women with normal pregnancy (control group). All study participants gave written informed consent, and the study procedures were approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2016-65).

Breast milk sampling

The breast milk samples were collected on postpartum days 1–3 (colostrum), on days 7–10 (transitional milk), and at 4 weeks (mature milk). The whole milk from each mother was obtained completely by pump expression in the morning of the sampling day before feeding the newborn. After each expression, the whole milk was homogenized via vortexing the tube for 30 seconds, and 6 mL of homogenized milk was transferred into sterile Eppendorf tubes in aliquots and immediately frozen at –80°C. The remainder of the milk was returned to the mothers for infant feeding.

Sample preparation for the GC-MS analysis

The samples were thawed on ice, and 300 µL of breast milk was transferred into a new sterile polypropylene tube. Four internal standards, which included 20 µL of DL-alanine-2, 3, 3, 3-d4 (Sigma, USA, 10 mM), DL-phenylalanine (CIL, USA, 10 mM), DL-tyrosine (CIL, USA, 10 mM), and octanoic acid (CIL, USA, 10 mM), were added into each tube and vortexed for 30 seconds, and then the samples were dried in a SpeedVac with a refrigerated vapor trap (Thermo Scientific, Auckland, New Zealand). The dried breast milk underwent cold methanol extraction using 50% and 80% v/v methanol/water. The samples were centrifuged (17 000 g/15 minute) at 4°C, and then the pooled supernatants were dried. The dried samples were stored at –20°C until derivatization. For the derivation, the samples were derivatized by methyl chloroformate alkylation. A pooled quality control (QC) sample was used to analyze the reproducibility and quantitative robustness and analyzed for each batch by taking 20 µL from each prepared sample within the batch. The QC sample was then run multiple times at the beginning of each batch, in between runs, and at the end of each batch. In addition, blanks were included to facilitate correction for background noise.

GC-MS analysis and data acquisition

A total of 552 human milk samples from 90 GDM patients and 94 controls were subjected to metabolomic analysis by using

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GC-MS (Agilent 5977A MSD system coupled to an Agilent 7890B GC system). The system was equipped with an Agilent 7693 autosampler. A ZB-1701 column (35 m, 0.25 mm ID, 0.15 µm df) was installed. 1 µL sample was injected into the system. The inlet was operated in split-less mode and maintained at 250°C throughout the experiment. The GC oven was initially set to 45°C and was held at that temperature for 2 minutes. The temperature was then ramped up to 180°C at a rate of 9°C/minute and held at that temperature for 5 minutes. The temperature was ramped up to 220°C at a rate of 40°C/minute and held at that temperature for 5 minutes. The temperature was then ramped up to 240°C at a rate of 40°C/minute and held at that temperature for 11.5 minutes. The temperature was further ramped up to 280°C at a rate of 40°C/minute and held at that temperature for 10 minutes. The total run time was 51 minutes. The single quadrupole MS was equipped with an EI source and was tuned on a daily basis. The metabolite identification by GC-MS was performed by searching the National Institute of Standards and Technology (NIST) database. The raw data were deconvoluted using the Automated Mass Spectral Deconvolution and Identification System (AMDIS) combined with in-house R-based software for metabolite identification and peak integration (relative quantification).

Statistical analysis

The statistical analyses were performed with SPSS version 17.0 software and R-based software. The clinical data (age, body mass index (BMI), birth weight, head circumference, and birth height) were compared using a *t*-test. The semi-quantitative log values of identified metabolites were provided in the GDM group and the control group by median (1^{st}–3^{st} quartile)/100 ML. Linear logistic regression comparisons between the control group and the GDM group of colostrum, transitional milk, and mature milk were performed by general linear model (GLM) [15], which was created by using logistic regression package in R to identify significant metabolites (*P*-value cut off ≤0.05). The linear logistic regression models were also adjusted to potential confounding factors including mother's age, gestational age, and maternal BMI. For the key metabolite selection, the integral values of the samples were imported into SIMCA-P+ 11.5 software (Umetrics, Umea, Sweden). An orthogonal partial least squares discriminant analysis (OPLS-DA) was applied to the unit variance (UV)-scaled spectral data to visualize the differences among colostrum, transitional milk, and mature milk [16,17]. The coefficient loading plots and variable importance in projection (VIP) of the OPLS-DA model were used to identify the spectral variables contributing to sample discrimination; a correlation coefficient of |VIP| >1 (equivalent to $P<0.05$) was used as a cutoff value [18]. The VIP scores ranked the components according to their importance for the observed separation. In all statistical analyses, a *P*-value <0.05 was considered to be statistically significant.

Results

Demographic and clinical characteristics

The clinical characteristics of the enrolled study participants are summarized in Supplementary Table 1. The maternal BMI was 21.55±2.66 and 20.55±2.06 kg/m^2 in the GDM group and the control group, respectively ($P<0.05$). Maternal weight gain during pregnancy in the GDM group (14.05±5.71 kg) was significantly lower than that in the control group (15.98±4.79 kg, $P<0.05$). The average maternal age was 28.67±4.23 years in the control group and 30.78±4.19 years in the GDM group ($P<0.001$). Meanwhile, the average gestational age was 39.50±1.17 weeks in the control group and 39.14±1.00 weeks in the GDM group ($P<0.05$). However, there were no significant differences in neonate birth weight, height, or head circumference between the GDM group and the control group.

Identified metabolites in human breast milk

A total of 187 metabolites were identified in the breast milk samples (Supplementary Table 2), including 4 alkanes, 17 amino acid derivatives, 21 amino acids, 22 saturated fatty acids, 29 unsaturated fatty acids, 8 TCA cycle intermediates, 3 cofactors or vitamins, 3 keto acids and derivatives, 1 glycolytic intermediate, 43 organic acids, and 36 organic compounds. The coefficient of variation (CV) for the QC samples was listed to analyze the reproducibility and the average values of CV score were 29.5, which indicated that the model is valid for the analysis (Supplementary Table 3).

Metabolites that were altered in the colostrum, transition milk, and mature milk of women with uncomplicated pregnancies

The OPLS-DA results demonstrated that $|R^2\gamma| > 0.5$ and $|Q^2| > 0.4$, which indicated that different metabolite profiles were found in colostrum, transition milk, and mature milk (Figure 1). The empirical *P*-value was less than 0.05, which reflected the reliability of the OPLS-DA model. The analysis of the OPLS-DA loading coefficient plots showed that 59 metabolites were identified as contributing to the differences among the metabolomic profiles of colostrum, transition, and mature milk in normal pregnancies (Figure 2).

According to the Human Metabolome Database (HMDB) and NIST database, the majority of amino acids, including all essential amino acids such as isoleucine, leucine, lysine, methionine, phenylalanine, tryptophan, valine, threonine, and derivatives, were increased in colostrum compared to transition milk and mature milk. Moreover, 6 out of the 7 different saturated fatty acids, including palmitic acid, margaric acid, myristic acid, dodecanoic acid, decanoic acid, and octanoic acid, were found

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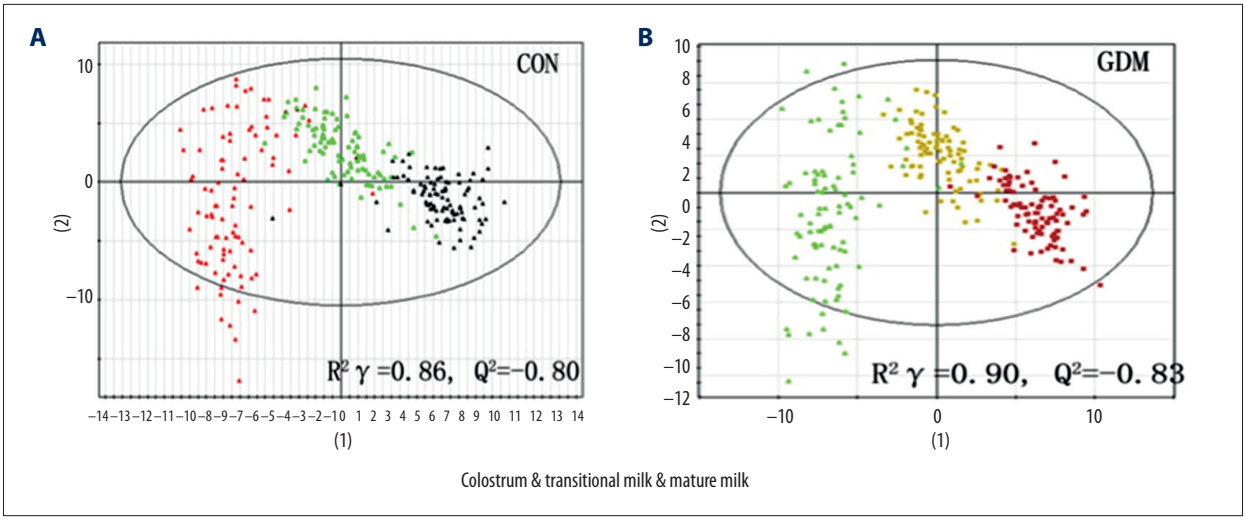

Figure 1. Metabolomic analysis of breast milk samples. (**A**) OPLS-DA score plots showing a clear separation among colostrum (red dots), transitional milk (green dots), and mature milk (black dots) in the control group. (**B**) OPLS-DA score plots showing a clear separation among colostrum (green dots), transitional milk (yellow dots), and mature milk (red dots) in the GDM group.

to be significantly lower in colostrum compared to transition milk; the levels of hexanoic acid were comparable between colostrum and transition milk but increased in mature milk. Of the 13 differing unsaturated fatty acids, palmitelaidic acid, oleic acid, cis vaccenic acid, conjugated linoleic acid, 9,12-octadecadienoic (Z, Z)-,2-hydroxy-1-(hydroxymethyl) ethyl ester, myristoleic acid, 3-hydroxydecanoic acid, and gamma linolenic acid were lower in colostrum, while 3-methyl-2-oxopentanoic acid, butanedioic acid, ethyl methyl ester, 4-methyl-2-oxopentanoic acid, 5-cyano-4-methoxyamino-7-phenyl-hept-6-enoic acid, methyl ester, (E,S)-2-hexenoic acid, 4-amino-5-methyl-methyl ester were higher in colostrum than in the other 2 milk types. Myristoleic acid, oleic acid, cis-vaccenic acid, and 5-cyano-4-methoxyamino-7-phenyl-hept-6-enoic acid were lower in mature milk compared with those in transition milk, while 3-hydroxydecanoic acid, (E,S)-2-hexenoic acid, and 4-amino-5-methyl-methyl ester were higher in mature milk compared with those in transition milk. The remaining 6 unsaturated fatty acids were less significantly different between mature milk and transition milk. Moreover, compared to the levels in the transition milk and mature milk, the levels of 2 TCA cycle intermediates, 2-oxoglutaric acid and isocitric acid were higher in colostrum, while the levels of citric acid and malic acid were lower in colostrum. For the class of cofactors and vitamins, the level of nicotinic acid was slightly lower in mature milk and NADP/NADPH was moderately higher in transition and mature milk than in colostrum.

Although the metabolome of transition milk was very similar to that of mature milk, notable discrepancies were also identified between these 2 groups. For instance, the TCA cycle intermediates, such as citric acid, isocitric acid, and 2-phosphoenolpyruvic acid, were increased in mature milk.

Metabolites that were altered in the colostrum, transition milk, and mature milk of women with GDM pregnancies

Similarly, in the GDM group, the OPLS-DA results demonstrated that $|R^2\gamma| > 0.5$ and $|Q^2| > 0.4$, indicating that different metabolite profiles were found among colostrum, transition milk, and mature milk (Figure 1). Fifty-eight metabolites were identified as contributing to the differences in the metabolomic profiles among the colostrum, transition, and mature milk of GDM pregnancies (Figure 3). The metabolome composition and differences among the colostrum, transition milk, and mature milk from GDM mothers shared many similarities with those from normal pregnancies. However, alterations in breast milk metabolome due to GDM were identified. For example, the levels of stearic acid, pentadecanoic acid, 9-heptadecanoic, and arachidic acid were significantly lower in GDM transition milk than in GDM colostrum (these fatty acids did not differ significantly between the colostrum and transitional milk from normal pregnancies). Moreover, there were significant differences in 9,12-octadecadienoic (Z,Z)-,2-hydroxy-1-(hydroxymethyl) ethyl ester and glutamine between colostrum and transition milk from normal pregnancies that were not identified in the GDM group.

Metabolites in the breast milk that showed the differences between GDM and uncomplicated pregnancies

To determine the detailed variations in metabolite enrichment between the GDM group and the control group, linear logistic regression analyses were performed (Figure 4). We found that most of the statistically differential metabolites were lower in the GDM group. In colostrum, 6 metabolites were significantly lower in the GDM group compared to the control group,

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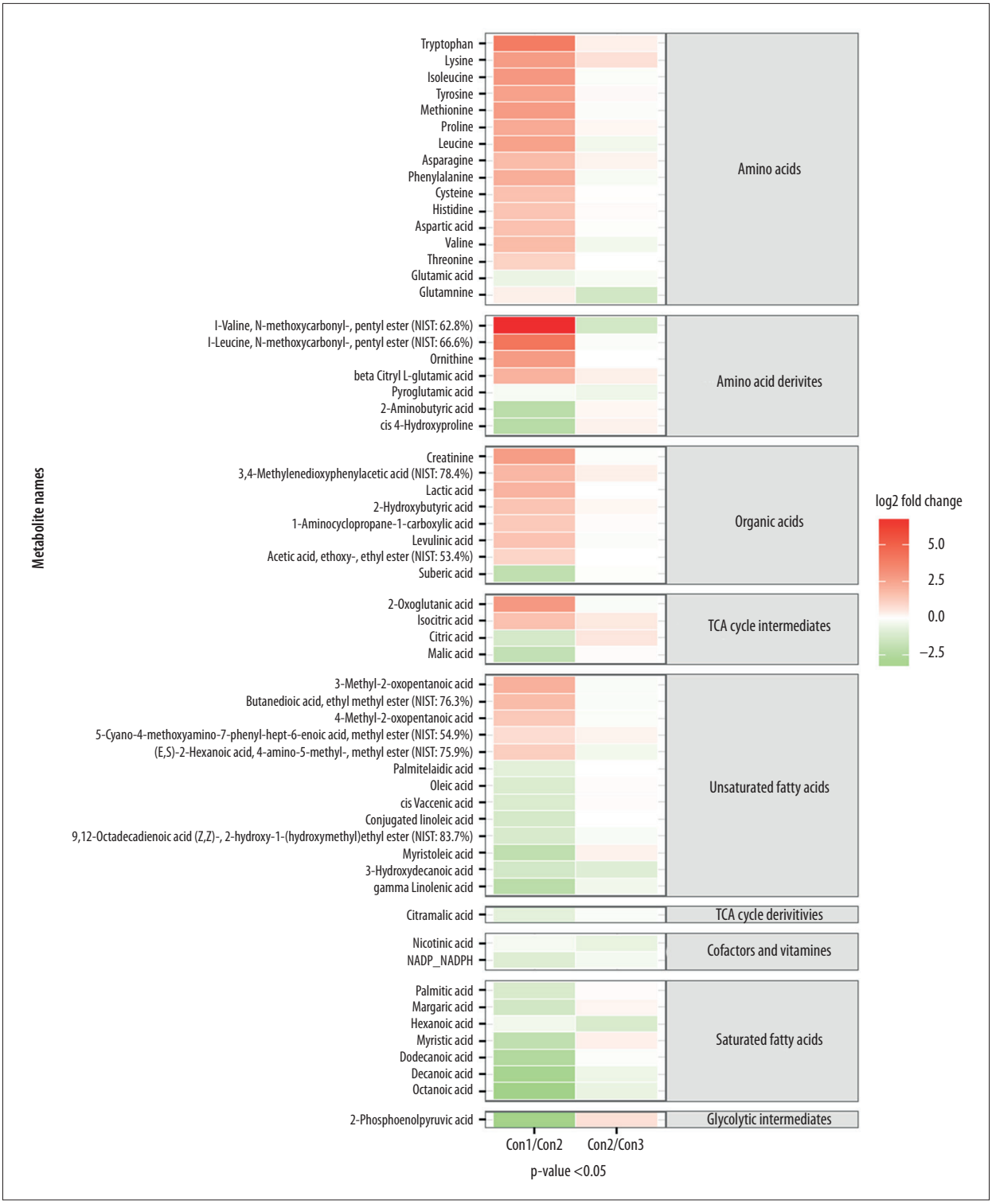

Figure 2. Heat Map of key metabolites that differed in colostrum, transitional milk, and mature milk in the uncomplicated pregnancy control group. Comparisons of colostrum versus transitional milk and transitional milk versus mature milk are depicted. Increased and decreased metabolite levels are depicted by red and green colors, respectively.

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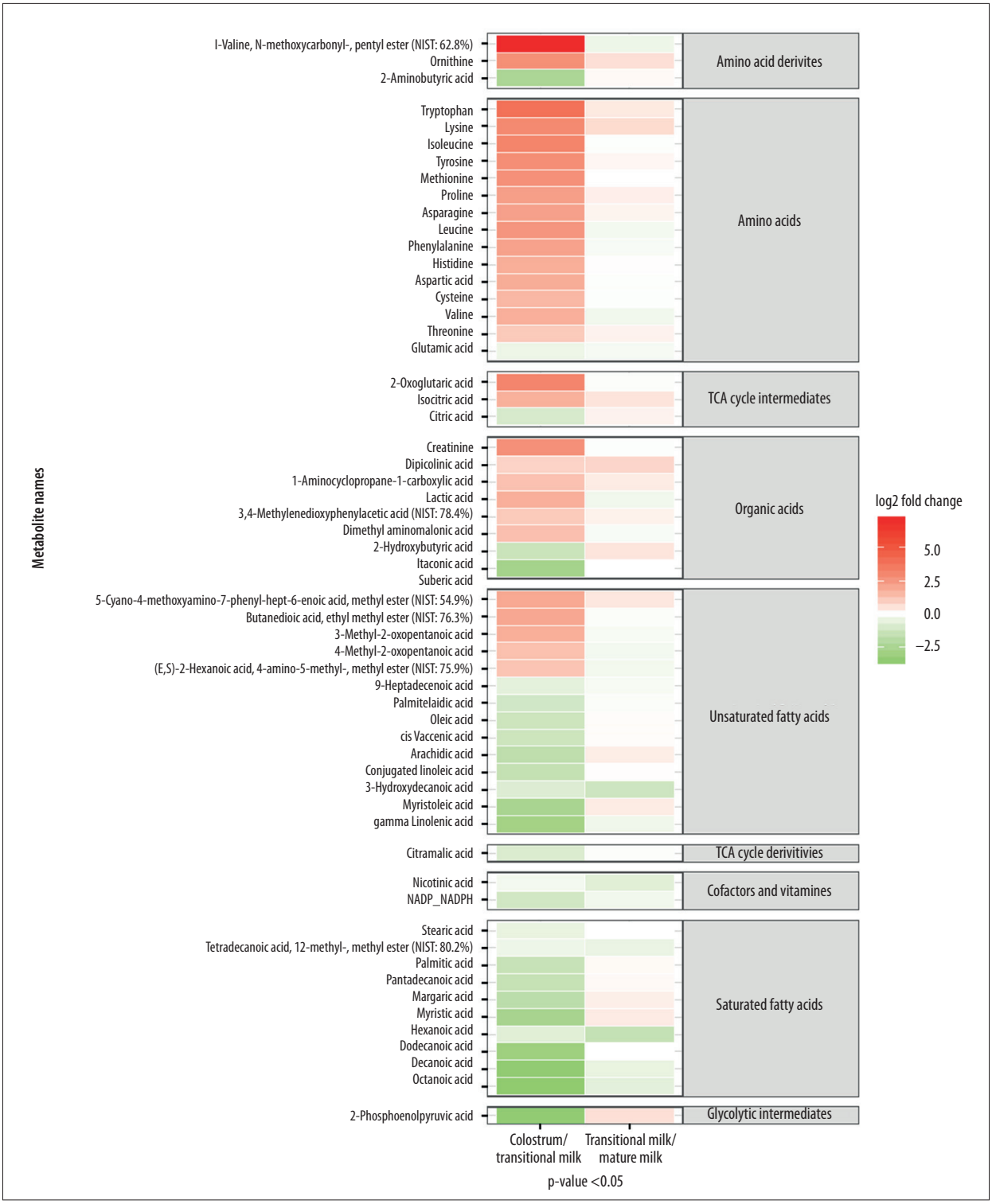

Figure 3. Heat Map of key metabolites that differed in colostrum, transitional milk, and mature milk in the GDM pregnancy group. Comparisons of colostrum versus transitional milk and transitional milk versus mature milk are depicted. Increased and decreased metabolite levels are depicted by red and green colors, respectively.

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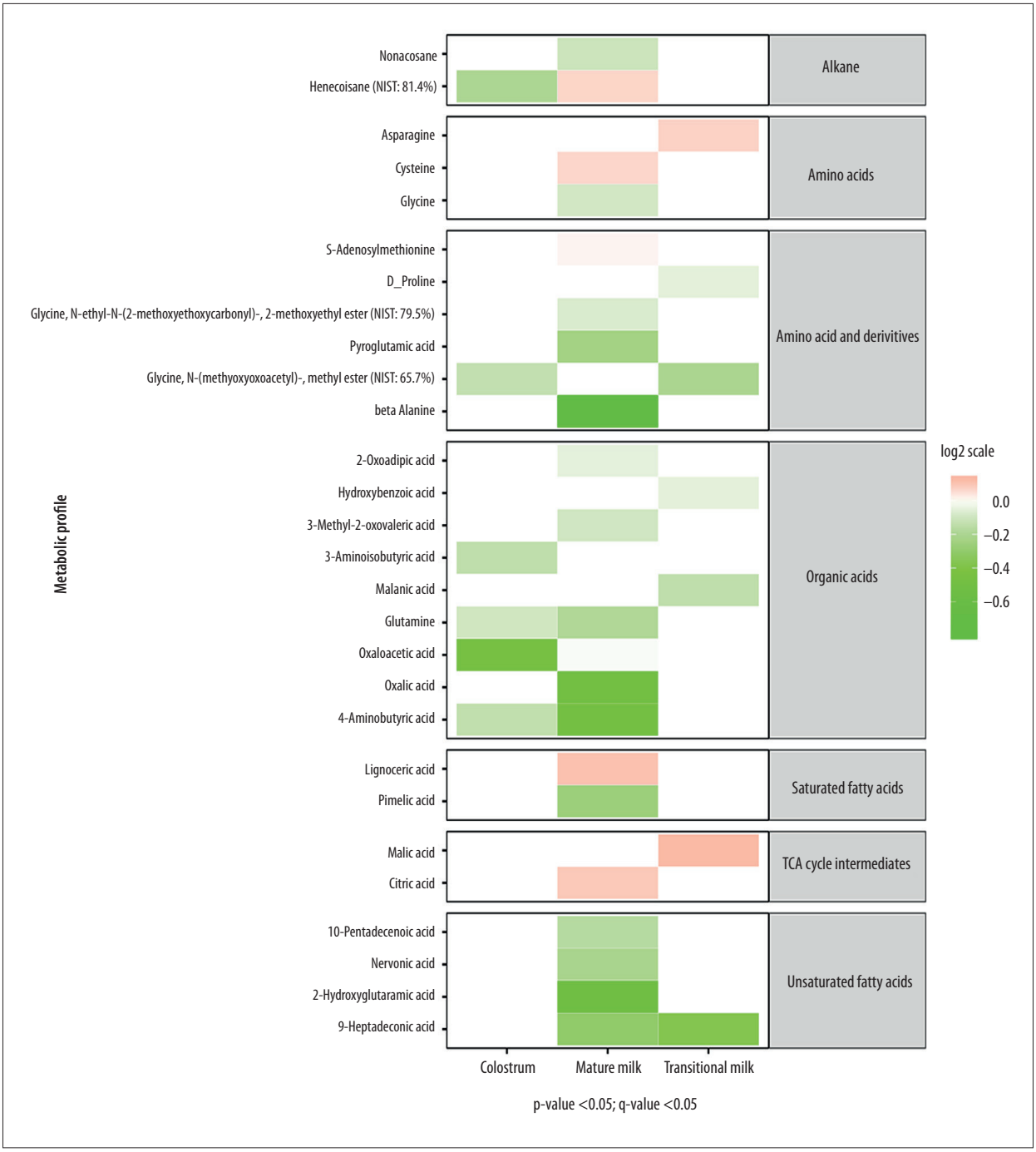

Figure 4. Linear logistic regression analysis of the metabolites in breast milk between the GDM group and the healthy control group. Red blocks indicate higher metabolite in the GDM group compare to the control group, whereas green blocks represent lower predicted metabolite levels in the GDM group compared to the control group. Only metabolites with *P*-value less than 0.05 and q-value were less than 0.15 (colostrum), 0.1 (transitional milk), or 0.05 (mature milk) are shown.

including 1 alkane [heneicosane (NIST: 81.4%)], 1 amino acid and derivatives [G\glycine, N-(methoxyoxoacetyl)-, methyl ester (NIST: 65.7%)] and 4 organic acids (3-aminoisobutyric acid, glutamine, oxaloacetic acid, and 4-aminobutyric acid). In transitional milk, 5 metabolites were reduced in the GDM group, including 2 amino acid and derivatives [D-proline, glycine, N-(methoxyoxoacetyl)-, methyl ester (NIST: 65.7%)], 2 organic acids (hydroxybenzoic acid, malonic acid) and 1 unsaturated fatty acid (9-heptadecenoic acid), while 1 amino acid (asparagine) and 1 TCA cycle intermediate (malic acid) were

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elevated in the GDM group. Importantly, there were 21 metabolites that were significantly different between these 2 groups. There were 17 metabolites that were significantly decreased in the GDM group compared with the control group, including 1 alkane (nonacosane), 1 amino acid (glycine), 3 amino acid and derivatives [glycine, N-ethyl-N-(2-methoxyethoxycarbonyl)-, and 2-methoxyethyl ester (NIST: 79.5%), pyroglutamic acid, beta-alanine], 6 organic acids (2-oxoadipic acid, 3-methyl-2-oxovaleric acid, 4-aminobutyric acid, glutamine, oxalic acid, and oxaloacetic acid), 1 saturated fatty acid (pimelic acid), 4 unsaturated fatty acids (9-heptadecenoic acid, 10-pentadecenoic acid, 2-hydroxyglutaramic acid, and nervonic acid), while 4 metabolites were significantly increased in the GDM group including 1 alkane [heneicosane (NIST: 81.4%)], 1 amino acid (cysteine), 1 saturated fatty acid (lignoceric), and 1 TCA cycle intermediate (malic acid).

Discussion

Although nuclear magnetic resonance (NMR) has been applied to investigate changes in maternal milk metabolome [19,20], GC-MS can provide more information [21]. According to Wishart [21], GC-MS can be used to identify and quantify a wide range of metabolites with relatively high sensitivity and reproducibility. However, with chemical derivatization participating, this process may possibly lead to an unsatisfying result by producing some by-products. Recently, GC-MS has been widely used in metabolomics such as cerebrospinal fluid metabolome, blood metabolome, and human breast milk metabolome [22–25].

In our study, we found that maternal age and BMI were higher in the GDM group than in the control group; which was consistent with results from previous studies [26,27]. Breast milk provides various essential nutrients and helps the immune system and organ development in neonates [8,28,29]. The components of human milk vary during lactation, particularly in the first month postpartum. Colostrum is rich in immunologic compounds and growth factors [30,31], while mature milk becomes stable to avoid further fluctuations [32]. In the present study, we analyzed the composition of the metabolites in breast milk at the different stages of lactation from GDM mothers and healthy controls.

Our data demonstrated that after normal pregnancies, 16 amino acids were increased in colostrum compared to transition and mature milk, including all essential amino acids and branched-chain amino acids (leucine, isoleucine, and valine). Free amino acids are an important source of nitrogen for the growing infant and are more readily absorbed than protein-derived amino acids [33]. Branched-chain amino acids are key nitrogen donors involved in interorgan and intercellular nitrogen shuttling, and leucine is an important nutrient signal [34,35]. Lysine is necessary for protein synthesis, and its deficiency has been found to cause weight loss in neonates [36]. Infants grow rapidly in the first months of life; therefore, high levels of amino acids in colostrum are likely to be a critical resource for neonatal development.

Fatty acids are known to be key to infant growth, brain development, and health [37]. Colostrum and mature milk contain 1.9–2.3% and 3.5–4.5% lipids, respectively [38]. We found increased levels of fatty acids in mature milk compared to those in colostrum, although hexanoic acid, which is a short-chain fatty acid widely used for parenteral nutrition in individuals requiring supplemental nutrition [39], was found to be increased in colostrum in our study. This enrichment of fatty acids in mature milk is likely to be important for infant development. Gamma-linolenic acid in breast milk might reduce the risk of mother-to-child transmission of HIV by breastfeeding [40]. High concentrations of long-chain fatty acids in breast milk, such as oleic acid, might have functional effects on the establishment of gut microbiota in early life [41].

It is known that the offspring of GDM mothers are at a higher risk type-2 diabetes [5]. Several studies have documented alterations in the plasma metabolome of women with GDM, either during pregnancy or postpartum, compared to that in women with uncomplicated pregnancies [42–44]. We found that the components of breast milk in healthy mothers were quite similar to those in GDM mothers as shown by OPLS-DA; most of the difference in milk composition ranging from colostrum to mature milk are subtle. Klein and colleagues reported that there was no significantly difference in free amino acids in breast milk between GDM patients and normal controls [45], while our study demonstrated that quite a lot of free fatty acids in breast milk significantly declined in the GDM group compare to the control group. Considering that both amino acids and free fatty acids are the major nutrients in human breast milk and important for neonatal development, the similarity in amino acids profiles implies that the discrepancies in free fatty acids profile might play a more profound role in breastfeeding related offspring developmental disorders or health-risks in later life. Since free fatty acids are the building blocks for adipogenesis and neurons, disturbed fatty acids composition in breast milk might compromise neonatal adiposity and brain development if breast fed. Therefore, fatty acids composition of formula should be carefully adjusted for infants conceived by GDM mothers.

Conclusions

The metabolomic profile of human milk is dynamic throughout the first month of lactation. High levels of amino acids in

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colostrum and high levels of saturated and unsaturated fatty acids in mature milk were features of breast milk from women in had both the normal pregnancy group and GDM pregnancy group. Although the composition of colostrum, transition milk, and mature milk was highly similar between these groups, the GDM group was associated with alterations in the metabolome of breast milk, especially colostrum, which might adversely influence the long-term health of offspring. Fatty acids-optimized formula might be a better choice than maternal breast milk for feeding GDM complicated newborns.

Conflicts of interest

None.

Supplementary Tables

Supplementary Table 1. Patient characteristics.

Characteristics	Controls (n=94)	GDM (n=90)	P value
Maternal age (years)	28.67±4.23	30.78±4.19	0.001*
Pregnancy BMI (kg/m^2)	20.55±2.06	21.55±2.66	0.005*
Gestational Age (week)	39.50±1.17	39.14±1.00	0.035*
OGGT fasting (mmol/L)	4.56±0.29	4.9±0.46	0.000*
OGGT 1-hour (mmol/L)	7.63±1.25	10.21±1.54	0.000*
OGGT 2-hour (mmol/L)	6.82±0.91	9.48±5.27	0.000*
Maternal weight gain at parturition (kg)	15.98±4.79	14.05±5.71	0.014*
Neonate birth weight (g)	3317.13±360.97	3373±384.966	0.311
Neonate birth head circumference (cm)	34.29±1.17	34.36±1.06	0.703
Neonate birth Height (cm)	49.72±1.68	49.71±1.60	0.977

Student *t*-test was used for statistical analysis. Adjusted significance value $P<0.05$(*).

Supplementary Table 2. The Semi-quantitative log values of identified metabolites were provided in the GDM group and the control group including colostrum, transitional milk, and mature milk (median, 1st–3rd quartile) per 100 mL.

Name	Classification	Control-colostrum-median (range)/ 100 mL	GDM-colostrum-median (range)/ 100 mL	Control-transitional milk-median (range)/ 100 mL	GDM-transitional milk-median (range)/ 100 mL	Control-mature milk-median (range)/ 100 mL	GDM-mature milk-median (range)/ 100 mL
Decane, 2-methyl (NIST: 64.4%)	Alkane	4.82 (4.65–4.99)	4.78 (4.62–4.97)	4.88 (4.83–5.08)	4.89 (4.72–5.05)	5.08 (4.93–5.22)	5.06 (4.92–5.25)
Dodecane	Alkane	5.19 (4.79–5.61)	5.27 (4.64–5.55)	5.55 (5.49–5.94)	5.77 (5.53–5.92)	5.87 (5.72–6)	5.88 (5.69–6.03)
Octadecane (NIST: 84.5%)	Alkane	5.75 (5.6–5.9)	5.76 (5.59–5.92)	5.8 (5.73–5.92)	5.85 (5.75–5.92)	5.87 (5.79–5.97)	5.83 (5.76–5.96)
Tricosane	Alkane	4.96 (4.83–5.09)	4.92 (4.81–5.02)	4.98 (4.92–5.16)	5.06 (4.95–5.18)	5.1 (4.95–5.21)	5.07 (4.96–5.18)
beta-Alanine	Amino acid derivatives	6.56 (6.36–6.67)	6.57 (6.39–6.71)	6.36 (6.08–6.34)	6.24 (6.11–6.36)	6.28 (6.11–6.39)	6.26 (6.14–6.44)
beta-Citryl,L-glutamic acid	Amino acid derivatives	4.63 (4.34–5.08)	4.61 (4.33–4.89)	4.29 (4.09–4.47)	4.24 (4.09–4.41)	4.22 (4.06–4.39)	4.24 (4.06–4.36)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

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cis-4-Hydroxyproline	Amino acid derivatives	5.87 (5.74–6.08)	5.92 (5.73–6.01)	6.23 (6.42–6.8)	6.63 (6.47–6.86)	6.51 (6.27–6.65)	6.5 (6.26–6.65)
D_Norvaline	Amino acid derivatives	5.27 (5.03–5.51)	5.06 (4.83–5.32)	5.22 (5.14–5.48)	5.18 (4.9–5.39)	5.13 (5.01–5.27)	5.07 (4.76–5.29)
D_Proline	Amino acid derivatives	5.9 (5.39–6.35)	5.6 (5.23–6.05)	5.8 (5.38–6.4)	5.67 (5.11–5.95)	6.03 (5.41–6.48)	5.78 (5.36–6.07)
D-Proline, N-methoxycarbonyl-, pentyl ester (NIST: 88.5%)	Amino acid derivatives	8.24 (8.06–8.35)	8.25 (8.14–8.37)	7.77 (7.41–7.58)	7.5 (7.38–7.64)	7.35 (7.26–7.48)	7.36 (7.22–7.47)
D-Prolyl-d-proline, N-methoxycarbonyl-, methyl ester (NIST: 92.1%)	Amino acid derivatives	6.39 (5.7–6.73)	6.55 (5.85–6.85)	5.22 (4.83–5.06)	4.93 (4.79–5.08)	4.96 (4.88–5.12)	4.94 (4.83–5.09)
Glycine, N-ethyl-N-(2-methoxyethoxycarbonyl)-, 2-methoxyethyl ester (NIST: 97.5%)	Amino acid derivatives	5.48 (5.36–5.62)	5.42 (5.32–5.54)	5.42 (5.36–5.5)	5.41 (5.33–5.49)	5.41 (5.35–5.49)	5.4 (5.33–5.47)
L-Isoleucine, N-methoxycarbonyl-, methyl ester (NIST: 91.1%)	Amino acid derivatives	7.93 (7.65–8.06)	7.99 (7.77–8.09)	7.31 (7.02–7.22)	7.13 (7.01–7.24)	7.19 (7–7.31)	7.21 (7.09–7.29)
L-Leucine, N-methoxycarbonyl-, pentyl ester (NIST: 66.6%)	Amino acid derivatives	6.49 (5.83–6.88)	6.57 (5.93–7.07)	5.63 (5.06–5.54)	5.26 (5.08–5.47)	5.22 (4.99–5.5)	5.16 (4.87–5.35)
L-Proline, N-methoxycarbonyl-, octyl ester (NIST: 77.3%)	Amino acid derivatives	6.38 (6.17–6.62)	6.41 (6.15–6.66)	6.46 (6.28–6.74)	6.45 (6.04–6.63)	6.58 (6.23–6.79)	6.46 (6.14–6.65)
L-Prolylglycine, N-methoxycarbonyl-, methyl ester (NIST: 85.7%)	Amino acid derivatives	6.73 (6.21–7.19)	6.86 (6.38–7.23)	5.97 (5.4–5.8)	5.62 (5.42–5.79)	5.52 (5.29–5.69)	5.49 (5.3–5.68)
L-Valine, N-methoxycarbonyl-, pentyl ester (NIST: 62.8%)	Amino acid derivatives	6.37 (5.61–6.84)	6.48 (5.69–7.08)	4.91 (4.49–4.71)	4.6 (4.43–4.76)	4.66 (4.5–4.84)	4.64 (4.49–4.82)
Norleucine	Amino acid derivatives	5.04 (4.83–5.22)	4.98 (4.72–5.15)	5.17 (5.18–5.31)	5.21 (5.11–5.28)	5.24 (5.16–5.3)	5.22 (5.1–5.28)
Norvaline	Amino acid derivatives	5.06 (4.9–5.26)	5.09 (4.86–5.3)	5 (4.77–5.09)	4.89 (4.68–5.02)	4.96 (4.83–5.12)	4.91 (4.68–5.06)
Pyroglutamic acid	Amino acid derivatives	7.67 (7.4–7.81)	7.7 (7.48–7.84)	7.71 (7.56–7.84)	7.71 (7.56–7.81)	7.88 (7.72–8)	7.88 (7.73–7.98)
S-Adenosylmethionine	Amino acid derivatives	6.23 (6.08–6.46)	6.32 (6.16–6.44)	6.32 (6.08–6.5)	6.3 (6.09–6.5)	6.38 (6.17–6.46)	6.31 (6.14–6.45)
Alanine	Amino acids	7.83 (7.65–7.96)	7.86 (7.72–7.98)	7.86 (7.75–7.95)	7.87 (7.76–7.97)	7.89 (7.81–7.98)	7.91 (7.81–7.99)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

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Asparagine	Amino acids	6.73 (6.28–7.06)	6.84 (6.38–7.15)	6.45 (6.12–6.49)	6.27 (6.16–6.45)	6.21 (6.06–6.41)	6.16 (6–6.35)
Aspartic acid	Amino acids	7.4 (7.11–7.71)	7.54 (7.26–7.77)	7.18 (6.93–7.16)	7.06 (6.92–7.14)	7.05 (6.85–7.19)	7.03 (6.9–7.2)
Cysteine	Amino acids	6.22 (5.97–6.6)	6.31 (5.96–6.63)	6.05 (5.81–6.13)	6.01 (5.84–6.14)	5.92 (5.79–6.06)	5.95 (5.78–6.12)
Glutamic acid	Amino acids	7.73 (7.59–7.84)	7.77 (7.62–7.87)	7.84 (7.81–7.99)	7.88 (7.82–7.98)	7.97 (7.87–8.04)	7.97 (7.89–8.03)
Glutamine	Amino acids	5.87 (5.7–6.04)	5.84 (5.67–6.04)	5.81 (5.61–5.95)	5.71 (5.54–5.89)	6.2 (5.93–6.38)	6.09 (5.91–6.3)
Glutathione	Amino acids	7.01 (6.77–7.41)	7.2 (6.92–7.42)	7.12 (6.9–7.2)	7.04 (6.93–7.19)	7.24 (7.11–7.39)	7.22 (7.11–7.34)
Glycine	Amino acids	7.43 (7.2–7.65)	7.39 (7.24–7.61)	7.27 (6.98–7.27)	7.1 (7.01–7.25)	7.28 (7.17–7.36)	7.27 (7.13–7.38)
Histidine	Amino acids	6.44 (6.17–6.74)	6.53 (6.26–6.81)	6.22 (5.95–6.21)	6.08 (5.95–6.16)	6.06 (5.92–6.19)	6.06 (5.92–6.17)
Isoleucine	Amino acids	7.28 (6.99–7.46)	7.38 (7.15–7.54)	6.63 (6.3–6.51)	6.42 (6.32–6.54)	6.39 (6.21–6.52)	6.4 (6.26–6.55)
Leucine	Amino acids	7.93 (7.65–8.06)	7.99 (7.77–8.09)	7.31 (7.02–7.22)	7.13 (7.01–7.24)	7.19 (7–7.31)	7.21 (7.09–7.29)
Lysine	Amino acids	7.84 (7.64–7.97)	7.89 (7.72–7.98)	7.35 (6.79–7.07)	6.89 (6.73–7.07)	6.64 (6.52–6.77)	6.6 (6.52–6.77)
Methionine	Amino acids	6.72 (6.46–6.87)	6.72 (6.52–6.88)	6.11 (5.71–5.99)	5.88 (5.74–6.02)	5.86 (5.7–6)	5.87 (5.75–6.02)
Ornithine	Amino acids	7.05 (6.68–7.38)	7.17 (6.84–7.42)	6.63 (6.16–6.48)	6.28 (6.15–6.4)	6.16 (6.04–6.33)	6.18 (6.06–6.28)
Phenylalanine	Amino acids	7.55 (7.22–7.66)	7.53 (7.28–7.69)	7.04 (6.78–6.95)	6.87 (6.8–6.94)	6.9 (6.78–7.03)	6.95 (6.84–7.02)
Proline	Amino acids	8.24 (8.06–8.35)	8.25 (8.14–8.37)	7.77 (7.41–7.58)	7.5 (7.38–7.64)	7.35 (7.26–7.48)	7.36 (7.22–7.47)
Serine	Amino acids	6.39 (6.22–6.6)	6.44 (6.25–6.7)	6.33 (6.13–6.39)	6.24 (6.08–6.33)	6.35 (6.18–6.47)	6.23 (6.11–6.45)
Threonine	Amino acids	7.36 (7.15–7.58)	7.45 (7.18–7.59)	7.2 (6.94–7.2)	7.06 (6.95–7.2)	7.05 (6.92–7.17)	7.02 (6.91–7.19)
Tryptophan	Amino acids	7.2 (6.87–7.4)	7.16 (6.79–7.44)	6.31 (5.85–6.15)	6.02 (5.8–6.22)	5.87 (5.68–6.04)	5.91 (5.73–6.08)
Tyrosine	Amino acids	7.39 (7.12–7.61)	7.5 (7.23–7.71)	6.86 (6.59–6.75)	6.69 (6.59–6.75)	6.56 (6.44–6.7)	6.56 (6.47–6.71)
Valine	Amino acids	7.92 (7.71–8.01)	7.93 (7.72–8.05)	7.53 (7.25–7.44)	7.38 (7.27–7.45)	7.44 (7.34–7.55)	7.45 (7.33–7.55)
NADP_NADPH	Cofactors and Vitamins	4.52 (4.39–4.73)	4.51 (4.39–4.61)	4.68 (4.74–5.03)	4.88 (4.75–5)	4.97 (4.83–5.07)	4.98 (4.88–5.08)
Nicotinamide	Cofactors and Vitamins	5.54 (5.39–5.72)	5.56 (5.39–5.68)	5.62 (5.57–5.78)	5.75 (5.65–5.84)	5.64 (5.55–5.76)	5.73 (5.6–5.82)

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Nicotinic acid	Cofactors and Vitamins	5.08 (4.94–5.23)	5.06 (4.88–5.24)	5.13 (4.98–5.38)	5.17 (5.03–5.38)	5.38 (5.28–5.51)	5.41 (5.3–5.55)
2-Phosphoenolpyruvic acid	Glycolytic interme-diates	4.77 (4.38–5.12)	4.6 (4.33–4.96)	5.56 (5.87–6.24)	6 (5.78–6.28)	5.89 (5.63–6.08)	5.89 (5.63–6.06)
3-Methyl,2-oxovaleric acid	Keto acids and derivatives	5.37 (5.21–5.5)	5.29 (5.2–5.48)	5.39 (5.33–5.5)	5.43 (5.32–5.52)	5.45 (5.35–5.55)	5.45 (5.34–5.54)
Oxaloacetic acid	Keto acids and derivatives	5.62 (5.07–6.06)	5.38 (5.03–5.82)	5.96 (6.01–6.25)	6.1 (5.94–6.21)	5.97 (5.8–6.12)	5.91 (5.74–6.06)
Pyruvic acid	Keto acids and derivatives	5.53 (5.39–5.74)	5.49 (5.31–5.66)	5.55 (5.44–5.75)	5.56 (5.37–5.65)	5.6 (5.45–5.75)	5.54 (5.35–5.66)
(1-Methyl-2,6-dioxocyclohexyl)acetic acid, methyl ester (NIST: 58.7%)	Organic acids	5.23 (4.93–5.58)	5.52 (5.07–5.79)	5.01 (4.53–4.93)	4.78 (4.55–5.02)	4.93 (4.67–5.14)	4.91 (4.7–5.24)
1-Aminocyclo-pentane-carboxylic acid, N-methoxy-carbonyl-, methyl ester (NIST: 51.1%)	Organic acids	5.36 (5.2–5.55)	5.38 (5.19–5.55)	5.23 (5.02–5.25)	5.12 (5.03–5.21)	5.21 (5.1–5.37)	5.19 (5.07–5.29)
1-Aminocyclopropane,1-carboxylic acid	Organic acids	4.98 (4.79–5.14)	5.02 (4.86–5.22)	4.78 (4.55–4.75)	4.64 (4.56–4.75)	4.63 (4.49–4.72)	4.55 (4.44–4.67)
2-(4-(2-Acetoxyethyl)-2,5-dimethoxyphenyl)acetic acid, methyl ester (NIST: 63%)	Organic acids	5.84 (5.63–6.11)	5.79 (5.62–6.1)	5.76 (5.59–5.89)	5.76 (5.62–5.87)	5.57 (5.37–5.82)	5.61 (5.41–5.76)
2-Aminobutyric acid	Organic acids	6.1 (5.91–6.28)	6.03 (5.78–6.24)	6.49 (6.62–7.04)	6.82 (6.63–7.03)	6.82 (6.62–6.96)	6.83 (6.62–6.97)
2-Hydroxybutyric acid	Organic acids	6.37 (6.17–6.53)	6.34 (6.16–6.5)	6.12 (5.79–6.06)	5.94 (5.82–6.08)	5.85 (5.74–6)	5.93 (5.77–6.07)
2-Hydroxyglutaramic acid	Organic acids	6.26 (6.05–6.43)	6.25 (6.09–6.44)	6.16 (5.92–6.25)	6.05 (5.96–6.22)	6.23 (6.11–6.36)	6.19 (6.07–6.33)
2-Hydroxyisobutyric acid	Organic acids	5.43 (5.24–5.65)	5.34 (5.14–5.6)	5.48 (5.45–5.64)	5.5 (5.42–5.6)	5.57 (5.49–5.73)	5.58 (5.49–5.65)
2-Oxoadipic acid	Organic acids	5.28 (5.11–5.46)	5.22 (5.07–5.43)	5.31 (5.14–5.64)	5.27 (5.11–5.43)	5.38 (5.07–5.63)	5.26 (5–5.44)
2-Oxomalonic acid, methylhydrazone, dimethyl ester (NIST: 62%)	Organic acids	6.03 (5.85–6.31)	6.07 (5.87–6.38)	5.95 (5.79–6.03)	5.89 (5.81–6.03)	6.03 (5.95–6.16)	6.03 (5.89–6.19)
2-Oxovaleric acid	Organic acids	5.6 (5.32–6.19)	5.65 (5.29–6.07)	5.53 (5.32–5.69)	5.45 (5.29–5.62)	5.81 (5.6–6)	5.91 (5.65–6.11)
2-Piperidinecarboxylic acid, 1-acetyl-, ethyl ester (NIST: 69.6%)	Organic acids	5.1 (4.96–5.3)	5.07 (4.89–5.23)	5.21 (5.2–5.42)	5.28 (5.15–5.4)	5.25 (5.12–5.39)	5.22 (5.11–5.34)
3,4-Methylenedio-xyphenylacetic acid (NIST: 78.4%)	Organic acids	5.33 (5.16–5.58)	5.37 (5.19–5.62)	5.05 (4.75–5)	4.85 (4.66–4.98)	4.73 (4.62–4.9)	4.71 (4.59–4.82)

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3-Aminoisobutyric acid	Organic acids	5.48 (5.36–5.61)	5.41 (5.3–5.54)	5.42 (5.33–5.5)	5.4 (5.32–5.49)	5.39 (5.32–5.49)	5.39 (5.29–5.45)
3-Furancarboxylic acid, methyl ester (NIST: 91.8%)	Organic acids	5.01 (4.8–5.19)	4.93 (4.79–5.16)	5.03 (4.96–5.26)	5.06 (4.94–5.19)	5.17 (5.02–5.32)	5.14 (5.03–5.27)
3-Hydroxy-azetidine-1-carboxylic acid, methyl ester (NIST: 65.9%)	Organic acids	5.85 (5.69–6.04)	5.78 (5.65–5.94)	5.93 (5.93–6.13)	6.01 (5.86–6.09)	5.86 (5.77–5.96)	5.84 (5.72–5.95)
4-Hydroxyphenylacetic acid	Organic acids	5.28 (5.1–5.43)	5.3 (5.14–5.47)	5.25 (5.04–5.37)	5.15 (5–5.3)	5.1 (4.97–5.25)	5.14 (5–5.34)
Acetic acid, 1-hydroxy-4,6-dimethyl-pyridin-2-ylmethyl ester (NIST: 59.2%)	Organic acids	5.46 (5.3–5.62)	5.43 (5.29–5.57)	5.49 (5.39–5.68)	5.4 (5.28–5.63)	5.59 (5.46–5.75)	5.54 (5.32–5.67)
alpha-Acetyllysine	Organic acids	5.03 (4.91–5.21)	5.02 (4.9–5.24)	5.01 (4.87–5.11)	4.97 (4.86–5.13)	5.02 (4.88–5.2)	5.01 (4.89–5.19)
Azelaic acid	Organic acids	6.26 (5.53–6.63)	6.15 (5.5–6.58)	6.64 (6.65–6.78)	6.7 (6.63–6.79)	6.59 (6.51–6.68)	6.6 (6.45–6.68)
Benzeneacetic acid, methyl ester (NIST: 88.3%)	Organic acids	5.06 (4.87–5.3)	5.03 (4.88–5.27)	4.98 (4.71–5.05)	4.84 (4.68–5.04)	4.94 (4.76–5.07)	4.98 (4.77–5.11)
Benzoic acid	Organic acids	5.64 (5.35–5.91)	5.56 (5.34–5.78)	5.8 (5.82–6.25)	6.05 (5.85–6.28)	5.96 (5.76–6.2)	5.94 (5.69–6.21)
Cabamic acid	Organic acids	4.96 (4.89–5.04)	4.89 (4.79–5.04)	4.92 (4.87–5.01)	4.94 (4.85–4.99)	4.96 (4.89–5.05)	4.93 (4.85–5.02)
Creatinine	Organic acids	6.25 (5.97–6.48)	6.41 (6.04–6.56)	5.75 (5.39–5.64)	5.55 (5.39–5.67)	5.56 (5.38–5.64)	5.56 (5.45–5.7)
Cyclohexanecarboxylic acid, 2-tridecyl ester (NIST: 53.2%)	Organic acids	5.18 (5.02–5.39)	5.15 (5.03–5.29)	5.2 (5.1–5.46)	5.27 (5.1–5.38)	5.35 (5.13–5.58)	5.26 (5.1–5.4)
D_Indole,3-butyric acid	Organic acids	5.2 (5.11–5.34)	5.24 (5.13–5.35)	5.18 (5.08–5.23)	5.13 (5.02–5.23)	5.19 (5.11–5.27)	5.18 (5.08–5.35)
Dehydroascorbic acid	Organic acids	6.75 (6.55–6.94)	6.64 (6.41–6.83)	6.9 (6.96–7.19)	7.01 (6.9–7.14)	6.89 (6.77–7.02)	6.9 (6.73–6.99)
Dipicolinic acid	Organic acids	4.94 (4.75–5.12)	4.94 (4.74–5.14)	4.75 (4.32–4.76)	4.55 (4.34–4.71)	4.28 (4.06–4.5)	4.17 (4.01–4.49)
Glutaric acid	Organic acids	4.59 (4.39–4.81)	4.56 (4.34–4.69)	4.65 (4.62–4.82)	4.69 (4.59–4.82)	4.68 (4.54–4.78)	4.71 (4.59–4.8)
Glyceric acid	Organic acids	5.81 (5.63–6)	5.72 (5.55–5.87)	5.84 (5.81–6.08)	5.91 (5.8–6.01)	5.95 (5.78–6.14)	5.94 (5.82–6.07)
Glyoxylic acid	Organic acids	5.78 (5.65–5.9)	5.73 (5.6–5.9)	5.75 (5.66–5.91)	5.77 (5.66–5.87)	5.79 (5.71–5.97)	5.8 (5.72–5.97)
Hippuric acid	Organic acids	5.57 (5.3–5.95)	5.61 (5.23–5.92)	5.8 (5.72–6.19)	5.81 (5.51–6.07)	5.79 (5.46–6.03)	5.69 (5.39–5.95)
Hydroxybenzoic acid	Organic acids	4.63 (4.48–4.75)	4.6 (4.42–4.76)	4.58 (4.48–4.68)	4.53 (4.45–4.64)	4.52 (4.44–4.62)	4.49 (4.4–4.59)
Lactic acid	Organic acids	7.8 (7.61–7.97)	7.73 (7.59–7.9)	7.43 (7.02–7.26)	7.13 (6.98–7.26)	7.03 (6.91–7.22)	7.09 (6.94–7.28)
Levulinic acid	Organic acids	4.64 (4.47–4.99)	4.76 (4.54–5.03)	4.51 (4.27–4.48)	4.38 (4.3–4.46)	4.42 (4.32–4.51)	4.38 (4.3–4.48)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

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Malonic acid	Organic acids	5.39 (5.2–5.52)	5.28 (5.18–5.46)	5.44 (5.43–5.58)	5.49 (5.41–5.56)	5.48 (5.38–5.57)	5.45 (5.37–5.54)
N-Ethylpyrrolidine-2,2-dicarboxilyc acid, dimethyl ester (NIST: 62.2%)	Organic acids	5.76 (5.49–6.01)	5.64 (5.45–5.95)	6.01 (6.04–6.23)	6.13 (5.99–6.25)	5.98 (5.88–6.09)	5.99 (5.84–6.1)
Oxalic acid	Organic acids	6.1 (5.78–6.48)	5.85 (5.53–6.18)	6.05 (5.9–6.4)	6.11 (5.51–6.28)	6.15 (5.95–6.4)	6.08 (5.73–6.3)
Phenethyl acetate	Organic acids	4.32 (4.1–4.48)	4.27 (4.04–4.47)	4.45 (4.28–4.56)	4.37 (4.23–4.54)	4.43 (4.33–4.66)	4.5 (4.35–4.65)
Propanedioic acid, methyl,ethyl ester (NIST: 64%)	Organic acids	5.1 (5.02–5.27)	5.14 (4.95–5.31)	5.12 (5.01–5.22)	5.06 (4.97–5.21)	5.15 (5.05–5.27)	5.11 (5.01–5.23)
Pyrrolidine-2-one-trans-4,5-dicarboxylic acid, dimethyl ester (NIST: 49.6%)	Organic acids	7.37 (7.13–7.54)	7.46 (7.34–7.55)	6.79 (6.43–6.6)	6.53 (6.4–6.65)	6.39 (6.29–6.5)	6.39 (6.26–6.51)
Stearic acid	Organic acids	7.76 (7.62–7.89)	7.77 (7.63–7.88)	7.87 (7.86–8.03)	7.94 (7.87–8)	7.92 (7.82–7.99)	7.91 (7.83–8.02)
Suberic acid	Organic acids	5.74 (5.53–6.16)	5.64 (5.5–6.14)	6.65 (6.84–7.09)	6.98 (6.86–7.11)	7 (6.86–7.13)	7.01 (6.83–7.12)
1-(2-Methoxyethoxy)-2-methyl-2-propanol, methyl ether (NIST: 63.2%)	Organic compounds	6.34 (6.2–6.52)	6.31 (6.11–6.48)	6.35 (6.21–6.52)	6.32 (6.13–6.49)	6.47 (6.31–6.63)	6.46 (6.27–6.59)
1,2-Hydrazinedicarboxylic acid, dimethyl ester (NIST: 58.3%)	Organic compounds	5.79 (5.49–6.02)	5.62 (5.4–5.84)	5.72 (5.56–6.19)	5.74 (5.51–6.01)	5.97 (5.52–6.26)	5.82 (5.49–6.07)
2-(1-Pentamethylphenyl) ethyl-3,3-diphenyloxaziridine (NIST: 67.9%)	Organic compounds	4.83 (4.68–5.04)	4.79 (4.61–4.96)	4.58 (4.33–4.52)	4.39 (4.28–4.49)	4.41 (4.29–4.56)	4.39 (4.27–4.5)
2,2-Dimethyl-tetrahydro-[1,3] dioxolo[4,5-c]pyran-6,7-diol (NIST: 60.3%)	Organic compounds	5.65 (5.38–5.91)	5.55 (5.34–5.81)	5.76 (5.72–6.05)	5.83 (5.65–6.04)	5.93 (5.66–6.07)	5.86 (5.64–5.97)
2,3-Furandione, dihydro-4,4-dimethyl (NIST: 91.3%)	Organic compounds	6.12 (5.68–6.5)	6.21 (5.64–6.56)	5.36 (4.93–5.21)	5.02 (4.89–5.19)	5.01 (4.88–5.18)	5.01 (4.82–5.15)
2-Acetonyl-9-[3-deoxy-β-d-ribouranosyl]hypoxanthine (NIST: 67.8%)	Organic compounds	4.92 (4.64–5.11)	4.79 (4.57–5.01)	4.96 (4.91–5.3)	4.95 (4.76–5.21)	5.1 (4.96–5.28)	5.02 (4.9–5.21)
2-Cyclohexylethanol, dimethyl(ethyl)silyl ether (NIST: 48%)	Organic compounds	5.43 (4.91–5.72)	5.23 (4.79–5.7)	5.79 (5.35–6.13)	5.65 (5.13–6.1)	5.83 (5.33–6.18)	5.61 (5.11–6.09)
2-Methoxy-N-(2-methoxy-propyl)-N-methyl-propionamide (NIST: 49.9%)	Organic compounds	4.97 (4.71–5.21)	5.06 (4.79–5.35)	4.91 (4.67–4.98)	4.86 (4.68–5.01)	4.95 (4.78–5.12)	4.97 (4.72–5.12)
3-Acetoxy,3-Hydroxy,2-methylpropionic acid	Organic compounds	5.75 (5.49–5.86)	5.65 (5.46–5.84)	5.75 (5.7–6)	5.79 (5.58–5.95)	5.89 (5.74–6.09)	5.8 (5.66–5.99)

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3H-Pyrazol-3-one, 2,4-dihydro-2,5-dimethyl- (NIST: 67.2%)	Organic compounds	5.19 (5–5.41)	5.18 (4.98–5.39)	5.02 (4.77–5.03)	4.9 (4.68–5.02)	5.05 (4.9–5.2)	4.95 (4.85–5.15)
3-Pyridinecarboxaldehyde (NIST: 90.7%)	Organic compounds	4.72 (4.58–4.9)	4.68 (4.48–4.83)	4.8 (4.74–5)	4.89 (4.76–5.01)	4.84 (4.72–4.94)	4.86 (4.73–4.97)
4,4-Dimethyl-5-methylene[1,3]dioxolan-2-one (NIST: 60.5%)	Organic compounds	5.02 (4.83–5.31)	5.11 (4.85–5.31)	4.82 (4.58–4.8)	4.65 (4.56–4.79)	4.76 (4.62–4.85)	4.71 (4.59–4.82)
4-Pyridinecarboxaldehyde (NIST: 83.6%)	Organic compounds	4.75 (4.56–4.96)	4.58 (4.45–4.79)	4.71 (4.61–5.1)	4.68 (4.47–4.87)	4.9 (4.56–5.06)	4.76 (4.49–4.91)
6,8-Dimethyl-7-phenyl-1,3,8-triazaspiro[4.5]decan-2,4-dithione (NIST: 41%)	Organic compounds	4.55 (4.43–4.73)	4.56 (4.4–4.7)	4.57 (4.47–4.71)	4.56 (4.41–4.67)	4.63 (4.46–4.74)	4.57 (4.39–4.66)
Acetophenone (NIST: 96.2%)	Organic compounds	4.57 (4.41–4.86)	4.56 (4.43–4.77)	4.65 (4.55–4.94)	4.67 (4.53–4.84)	4.7 (4.52–4.96)	4.71 (4.52–4.86)
BHT	Organic compounds	4.6 (4.16–5.06)	4.69 (4.41–4.98)	4.73 (4.46–5.27)	5 (4.7–5.3)	4.33 (4.19–4.56)	4.38 (4.22–4.74)
Bis(2-ethylhexyl) phthalate (NIST: 96.3%)	Organic compounds	5.85 (5.67–6.03)	5.7 (5.54–5.92)	5.85 (5.75–6.09)	5.85 (5.68–6.05)	5.94 (5.73–6.08)	5.89 (5.74–6.02)
Butanedioyl dihydrazide (NIST: 70.6%)	Organic compounds	6.96 (6.81–7.12)	6.96 (6.78–7.1)	7.04 (7–7.16)	7.08 (6.99–7.17)	7.06 (6.96–7.14)	7.08 (7–7.17)
Caffeine	Organic compounds	4.57 (4.38–4.85)	4.5 (4.3–4.68)	4.46 (4.33–4.59)	4.39 (4.27–4.53)	4.51 (4.36–4.71)	4.47 (4.35–4.68)
Cycloheptasiloxane, tetradecamethyl- (NIST: 94.2%)	Organic compounds	5.69 (5.52–5.86)	5.68 (5.46–5.9)	5.68 (5.48–5.81)	5.66 (5.42–5.81)	5.7 (5.53–5.89)	5.65 (5.48–5.86)
Cyclononasiloxane, octadecamethyl- (NIST: 91.7%)	Organic compounds	5.52 (5.34–5.8)	5.47 (5.2–5.73)	5.6 (5.47–5.87)	5.71 (5.48–5.84)	5.67 (5.46–5.89)	5.66 (5.49–5.84)
Cyclopentane, hexyl- (NIST: 65.9%)	Organic compounds	5.5 (5.26–5.75)	5.41 (5.17–5.6)	5.56 (5.55–5.93)	5.65 (5.52–5.81)	5.77 (5.58–6.12)	5.68 (5.47–5.92)
Cyclopentylamine, N-tert-butyldimethylsilyl (NIST: 52.6%)	Organic compounds	5.86 (5.6–6.08)	5.97 (5.57–6.2)	5.23 (4.78–5.1)	4.93 (4.73–5.08)	4.86 (4.69–5.03)	4.82 (4.66–5.05)
DBP	Organic compounds	5.21 (5.03–5.32)	5.21 (5.08–5.36)	5.24 (5.13–5.38)	5.31 (5.15–5.44)	5.3 (5.14–5.38)	5.3 (5.15–5.47)
Dehydroabietic acid	Organic compounds	4.44 (4.31–4.61)	4.38 (4.21–4.51)	4.44 (4.39–4.57)	4.47 (4.37–4.56)	4.51 (4.43–4.59)	4.5 (4.41–4.58)
Dimethyl ethylidenemalonate (NIST: 80.4%)	Organic compounds	5.79 (5.23–6.15)	5.64 (5.2–5.99)	6.14 (6.18–6.35)	6.25 (6.16–6.33)	6.11 (6.04–6.2)	6.12 (6–6.2)
Furyl hydroxymethyl ketone (NIST: 88.1%)	Organic compounds	5.01 (4.8–5.19)	4.93 (4.79–5.16)	5.03 (4.96–5.26)	5.06 (4.94–5.19)	5.17 (5.02–5.32)	5.14 (5.03–5.27)
Heptacosane (NIST: 78.9%)	Organic compounds	5.37 (5.19–5.59)	5.27 (5.13–5.55)	5.4 (5.36–5.61)	5.39 (5.24–5.59)	5.56 (5.37–5.68)	5.45 (5.31–5.63)
Methyl 2-ethoxyacetate (NIST: 64.4%)	Organic compounds	7.49 (7.25–7.75)	7.41 (7.22–7.66)	7.7 (7.7–7.91)	7.77 (7.65–7.86)	7.84 (7.71–7.93)	7.78 (7.67–7.88)

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Methyl 2-methylhexanoate (NIST: 70.4%)	Organic compounds	5.57 (5.25–5.73)	5.51 (5.29–5.75)	5.59 (5.39–5.8)	5.57 (5.33–5.79)	5.67 (5.46–5.88)	5.65 (5.4–5.79)
N(1-Methoxycarbonyl-1-methyl)ethyl-2-aza-1,3-dioxane (NIST: 87.4%)	Organic compounds	5.24 (5.11–5.34)	5.22 (5.14–5.36)	5.21 (5.12–5.29)	5.21 (5.12–5.29)	5.25 (5.17–5.33)	5.26 (5.19–5.37)
O-Acetylmalic anhydride	Organic compounds	5.7 (5.02–6.14)	5.28 (4.68–5.82)	5.76 (5.48–6.67)	5.79 (5.09–6.25)	6.18 (5.62–6.66)	5.86 (5.13–6.26)
Oxetane, 2,3,4-trimethyl-, (2α,3α,4β)- (NIST: 64.2%)	Organic compounds	4.81 (4.71–4.93)	4.81 (4.69–4.9)	4.71 (4.56–4.72)	4.63 (4.52–4.71)	4.68 (4.61–4.78)	4.71 (4.58–4.8)
Paraldehyde (NIST: 69.9%)	Organic compounds	6.1 (5.77–6.53)	6.08 (5.7–6.47)	6.1 (5.89–6.38)	6.06 (5.88–6.33)	6.44 (6.17–6.72)	6.55 (6.16–6.77)
Putrescine	Organic compounds	6.42 (6.22–6.73)	6.35 (6.2–6.53)	6.8 (6.86–6.98)	6.94 (6.88–7)	6.9 (6.82–6.96)	6.9 (6.81–6.97)
Trimethyl 2-methoxypropane-1,2,3-tricarboxylate (NIST: 60.4%)	Organic compounds	6.68 (6.02–7.05)	6.45 (6.14–6.93)	7.04 (7.07–7.28)	7.17 (7.05–7.28)	7.02 (6.91–7.12)	7.05 (6.9–7.14)
2-Methyloctadecanoic acid	Saturated fatty acids	5.14 (4.87–5.4)	5.21 (4.89–5.46)	5.21 (5.03–5.43)	5.16 (4.98–5.3)	5.18 (5.02–5.4)	5.17 (4.94–5.3)
3-Hydroxydecanoic acid	Saturated fatty acids	4.99 (4.89–5.17)	4.98 (4.81–5.16)	5.28 (5.32–5.63)	5.41 (5.31–5.57)	5.79 (5.6–5.94)	5.85 (5.61–6.05)
4-Aminobutyric acid (GABA)	Saturated fatty acids	6.1 (5.99–6.21)	6.05 (5.95–6.18)	6.13 (6.1–6.23)	6.17 (6.06–6.22)	6.21 (6.15–6.28)	6.19 (6.12–6.25)
Adipic acid	Saturated fatty acids	5.15 (5.03–5.27)	5.12 (4.96–5.24)	5.08 (4.97–5.13)	5.05 (4.93–5.14)	5.17 (5.09–5.26)	5.14 (5.03–5.22)
Arachidic acid	Saturated fatty acids	5.48 (5.27–5.73)	5.36 (5.15–5.7)	5.74 (5.81–6.24)	6.02 (5.81–6.21)	5.97 (5.75–6.09)	5.88 (5.75–6.12)
Behenic acid	Saturated fatty acids	4.68 (4.43–4.96)	4.59 (4.33–4.87)	5.16 (4.85–5.43)	5.11 (4.78–5.43)	5.05 (4.77–5.25)	5.01 (4.75–5.31)
Butanoic acid, 3-(ethylthio)- (NIST: 58.7%)	Saturated fatty acids	5.26 (5.11–5.46)	5.19 (5.03–5.38)	5.26 (5.13–5.48)	5.28 (5.12–5.38)	5.36 (5.17–5.51)	5.3 (5.13–5.44)
Decanoic acid	Saturated fatty acids	6.2 (5.96–6.52)	6.23 (5.95–6.47)	7.1 (7.34–7.72)	7.54 (7.38–7.66)	7.71 (7.61–7.83)	7.74 (7.55–7.9)
Dodecanoic acid	Saturated fatty acids	6.78 (6.56–7.13)	6.71 (6.57–7.1)	7.69 (7.9–8.13)	8.03 (7.93–8.14)	8.05 (7.92–8.15)	8.05 (7.9–8.15)
Hexanoic acid	Saturated fatty acids	6.23 (5.88–6.65)	6.18 (5.76–6.49)	6.39 (6.32–6.9)	6.51 (6.28–6.87)	6.93 (6.63–7.18)	7.03 (6.57–7.31)
Lignoceric acid	Saturated fatty acids	4.18 (4.04–4.38)	4.15 (4.05–4.35)	4.28 (4.1–4.52)	4.27 (4.1–4.53)	4.18 (4.05–4.35)	4.24 (4.12–4.34)
Margaric acid	Saturated fatty acids	5.87 (5.67–6.14)	5.81 (5.6–6.01)	6.23 (6.34–6.62)	6.49 (6.34–6.61)	6.42 (6.25–6.58)	6.39 (6.28–6.53)
Myristic acid	Saturated fatty acids	6.95 (6.75–7.35)	6.87 (6.65–7.18)	7.66 (7.85–8.08)	7.98 (7.81–8.12)	7.89 (7.75–8)	7.85 (7.67–7.99)
Nonadecanoic acid	Saturated fatty acids	4.94 (4.76–5.15)	4.88 (4.68–5.04)	5.1 (5.13–5.4)	5.24 (5.11–5.37)	5.22 (5.09–5.32)	5.17 (5.03–5.32)
Octanoic acid	Saturated fatty acids	5.84 (5.58–6.08)	5.74 (5.47–6.14)	6.54 (6.88–7.36)	7.1 (6.82–7.29)	7.27 (7.08–7.55)	7.35 (7–7.59)

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Palmitic acid	Saturated fatty acids	7.63 (7.44–7.92)	7.58 (7.46–7.76)	8 (8.06–8.17)	8.14 (8.07–8.2)	8.09 (8.02–8.15)	8.09 (8.01–8.16)
Pentadecanoic acid	Saturated fatty acids	5.9 (5.64–6.13)	5.75 (5.62–5.98)	6.14 (6.18–6.47)	6.35 (6.21–6.49)	6.27 (6.13–6.41)	6.27 (6.13–6.46)
Pimelic acid	Saturated fatty acids	4.65 (4.48–4.85)	4.58 (4.37–4.82)	4.58 (4.48–4.72)	4.49 (4.38–4.6)	4.63 (4.55–4.75)	4.59 (4.49–4.76)
Tetradecanoic acid, 12-methyl-, methyl ester (NIST: 80.2%)	Saturated fatty acids	5.34 (5.19–5.55)	5.27 (5.05–5.53)	5.38 (5.29–5.58)	5.44 (5.29–5.57)	5.57 (5.46–5.74)	5.58 (5.37–5.75)
Tridecanoic acid	Saturated fatty acids	5.67 (5.44–5.87)	5.59 (5.23–5.78)	5.76 (5.72–6.09)	5.87 (5.73–6.11)	5.76 (5.57–5.89)	5.78 (5.58–5.9)
Tridecanoic acid, 12-methyl-, methyl ester (NIST: 89.6%)	Saturated fatty acids	5.12 (4.93–5.29)	5.06 (4.84–5.21)	5.08 (5.01–5.21)	5.14 (5.01–5.25)	5.16 (5.02–5.32)	5.14 (5–5.3)
Undecanoic acid	Saturated fatty acids	5.31 (4.93–5.61)	5.29 (4.8–5.61)	5.44 (5.33–5.64)	5.51 (5.38–5.66)	5.5 (5.37–5.61)	5.52 (5.4–5.66)
2-Oxoglutaric acid	TCA cycle interme-diates	6.68 (6.48–6.81)	6.66 (6.46–6.82)	6.57 (6.34–6.64)	6.47 (6.3–6.6)	6.71 (6.55–6.81)	6.63 (6.49–6.74)
cis-Aconitic acid	TCA cycle interme-diates	6.92 (6.29–7.29)	6.7 (6.27–7.17)	7.27 (7.33–7.55)	7.41 (7.27–7.5)	7.25 (7.16–7.37)	7.26 (7.11–7.37)
Citramalic acid	TCA cycle interme-diates	5.7 (5.41–6.01)	5.61 (5.35–5.86)	5.88 (5.91–6.2)	5.97 (5.81–6.12)	6.08 (5.92–6.25)	6.02 (5.84–6.18)
Citric acid	TCA cycle interme-diates	8.17 (7.6–8.45)	8.06 (7.56–8.37)	8.42 (8.44–8.55)	8.49 (8.43–8.55)	8.44 (8.38–8.51)	8.43 (8.36–8.5)
Fumaric acid	TCA cycle interme-diates	5.9 (5.72–6.12)	5.8 (5.61–5.99)	6 (6.01–6.22)	6.08 (5.97–6.22)	5.98 (5.86–6.07)	5.96 (5.85–6.08)
Isocitric acid	TCA cycle interme-diates	5.98 (5.85–6.2)	6.01 (5.78–6.15)	6.04 (5.95–6.16)	6.08 (5.93–6.19)	5.84 (5.7–5.94)	5.84 (5.71–5.94)
Malic acid	TCA cycle interme-diates	6.38 (6.08–6.72)	6.26 (6.07–6.51)	6.78 (7.02–7.25)	7.15 (7–7.27)	7.14 (7.02–7.23)	7.12 (6.95–7.21)
Succinic acid	TCA cycle interme-diates	6.98 (6.82–7.13)	6.98 (6.8–7.1)	7.06 (7.02–7.18)	7.09 (7.01–7.18)	7.08 (6.99–7.15)	7.08 (7.01–7.18)
(E,S)-2-Hexenoic acid, 4-amino-5-methyl-, methyl ester (NIST: 75.9%)	Unsaturated fatty acids	5.34 (5.13–5.58)	5.34 (5.17–5.57)	5.16 (4.95–5.16)	4.96 (4.83–5.14)	5.13 (4.95–5.3)	5.06 (4.91–5.2)
10-Pentadecenoic acid	Unsaturated fatty acids	5.4 (5.21–5.59)	5.3 (5.12–5.5)	5.39 (5.33–5.73)	5.39 (5.23–5.57)	5.52 (5.31–5.81)	5.42 (5.21–5.64)
11,14-Eicosadienoic	Unsaturated fatty acids	5.94 (5.69–6.25)	5.82 (5.56–6.12)	6.18 (6.24–6.64)	6.42 (6.25–6.59)	6.19 (5.99–6.36)	6.16 (6.03–6.32)
13,16-Docosadienoic acid	Unsaturated fatty acids	5.23 (4.84–5.49)	5.06 (4.79–5.35)	5.37 (5.4–5.85)	5.56 (5.3–5.88)	5.65 (5.31–5.88)	5.57 (5.34–5.77)

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Name	Classification	Control-colostrum-median (range)/ 100 mL	GDM-colostrum-median (range)/ 100 mL	Control-transitional milk-median (range)/ 100 mL	GDM-transitional milk-median (range)/ 100 mL	Control-mature milk-median (range)/ 100 mL	GDM-mature milk-median (range)/ 100 mL
14-Methylpentadec-9-enoic acid methyl este r (NIST: 70.8%)	Unsaturated fatty acids	6.23 (6.05–6.42)	6.22 (6.05–6.43)	6.35 (6.32–6.52)	6.44 (6.2–6.53)	6.42 (6.18–6.51)	6.42 (6.09–6.49)
3-Hydroxyoctanoic acid	Unsaturated fatty acids	5.97 (5.66–6.26)	5.75 (5.49–6.17)	6.06 (6.02–6.41)	6.09 (5.87–6.24)	6.27 (5.98–6.44)	6.12 (5.84–6.29)
3-Methyl,2-oxopentanoic acid	Unsaturated fatty acids	5.65 (5.43–5.84)	5.68 (5.51–5.89)	5.27 (4.99–5.18)	5.12 (5–5.26)	5.06 (4.95–5.17)	5.09 (4.98–5.23)
4-Methyl,2-oxopentanoic acid	Unsaturated fatty acids	5.78 (5.64–5.96)	5.81 (5.65–5.98)	5.58 (5.31–5.55)	5.42 (5.31–5.55)	5.46 (5.33–5.58)	5.45 (5.3–5.59)
5-Cyano-4-methoxyamino-7-phenyl-hept-6-enoic acid, methyl ester (NIST: 54.9%)	Unsaturated fatty acids	5.94 (5.74–6.12)	6 (5.75–6.24)	5.85 (5.7–5.92)	5.83 (5.67–5.94)	5.74 (5.56–5.86)	5.68 (5.54–5.82)
9,12-Octadecadienoic acid (Z,Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester (NIST: 83.7%)	Unsaturated fatty acids	4.9 (4.74–5.13)	4.91 (4.69–5.04)	5.09 (5.15–5.48)	5.32 (5.18–5.48)	5.37 (5.18–5.58)	5.32 (5.17–5.53)
9-Heptadecenoic acid	Unsaturated fatty acids	5.53 (5.32–5.72)	5.45 (5.25–5.62)	5.56 (5.52–5.91)	5.69 (5.5–5.79)	5.73 (5.52–5.94)	5.71 (5.57–5.86)
Adrenic acid	Unsaturated fatty acids	5.73 (5.34–6)	5.6 (5.29–5.84)	6.05 (6.19–6.6)	6.44 (6.14–6.66)	5.99 (5.79–6.19)	6.1 (5.85–6.23)
alpha-Linolenic acid	Unsaturated fatty acids	5.12 (4.95–5.41)	5.03 (4.79–5.22)	5.33 (5.36–6.07)	5.59 (5.33–5.89)	5.84 (5.58–6.14)	5.81 (5.52–6.2)
Arachidonic acid	Unsaturated fatty acids	6.43 (6.22–6.65)	6.32 (6.16–6.51)	6.56 (6.63–6.92)	6.76 (6.65–6.88)	6.5 (6.35–6.64)	6.51 (6.37–6.67)
But-2-enedioic acid, dimethyl ester (NIST: 86.5%)	Unsaturated fatty acids	5.88 (5.75–6)	5.81 (5.68–5.93)	5.9 (5.87–6.08)	5.96 (5.81–6.05)	5.84 (5.73–5.93)	5.82 (5.73–5.95)
Butanedioic acid, dimethyl ester (NIST: 76.5%)	Unsaturated fatty acids	5.88 (5.72–6.13)	5.92 (5.66–6.12)	5.92 (5.85–6.06)	5.94 (5.8–6.05)	5.96 (5.87–6.05)	5.96 (5.86–6.03)
Butanedioic acid, ethyl methyl ester (NIST: 76.3%)	Unsaturated fatty acids	5.72 (5.49–5.92)	5.84 (5.57–6.05)	5.4 (5.21–5.35)	5.29 (5.2–5.36)	5.32 (5.22–5.4)	5.33 (5.26–5.39)
cis-Vaccenic acid	Unsaturated fatty acids	7.25 (7.1–7.55)	7.21 (7.07–7.4)	7.63 (7.66–7.77)	7.73 (7.67–7.78)	7.7 (7.65–7.75)	7.7 (7.63–7.76)
Conjugated-linoleic acid	Unsaturated fatty acids	7.25 (7.07–7.59)	7.23 (7.06–7.4)	7.71 (7.76–7.87)	7.83 (7.76–7.9)	7.82 (7.78–7.87)	7.82 (7.75–7.89)
DHA	Unsaturated fatty acids	5.73 (5.34–6)	5.6 (5.29–5.84)	6.05 (6.19–6.6)	6.44 (6.14–6.66)	5.99 (5.79–6.19)	6.1 (5.85–6.23)
Erucic acid	Unsaturated fatty acids	5.35 (5.01–5.6)	5.2 (4.94–5.51)	5.54 (5.58–6.02)	5.78 (5.48–6.1)	5.67 (5.44–5.93)	5.58 (5.38–5.91)
gamma-Linolenic acid	Unsaturated fatty acids	6.08 (5.77–6.51)	5.91 (5.66–6.31)	6.58 (6.76–7.19)	7.04 (6.82–7.22)	7.16 (7.02–7.25)	7.14 (6.94–7.26)
Gondoic acid	Unsaturated fatty acids	5.82 (5.6–6.12)	5.76 (5.48–6)	6.1 (6.17–6.57)	6.31 (6.2–6.51)	6.08 (5.9–6.26)	6.06 (5.93–6.27)
Itaconic acid	Unsaturated fatty acids	6.64 (6.04–6.95)	6.46 (5.98–6.79)	6.91 (6.94–7.12)	7.02 (6.93–7.09)	6.88 (6.8–6.95)	6.87 (6.75–6.97)

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Name	Classification	Control-colostrum-median (range)/ 100 mL	GDM-colostrum-median (range)/ 100 mL	Control-transitional milk-median (range)/ 100 mL	GDM-transitional milk-median (range)/ 100 mL	Control-mature milk-median (range)/ 100 mL	GDM-mature milk-median (range)/ 100 mL
Linolelaidic acid	Unsaturated fatty acids	6.06 (5.85–6.24)	5.94 (5.66–6.28)	6.23 (6.22–6.42)	6.3 (6.16–6.39)	6.36 (6.27–6.47)	6.34 (6.26–6.44)
Myristoleic acid	Unsaturated fatty acids	6.23 (6.04–6.6)	6.16 (5.95–6.47)	6.93 (7.1–7.35)	7.25 (7.08–7.39)	7.15 (7.01–7.27)	7.12 (6.94–7.26)
Nervonic acid	Unsaturated fatty acids	4.75 (4.58–4.97)	4.69 (4.51–4.93)	4.75 (4.49–4.94)	4.69 (4.47–4.96)	4.68 (4.51–4.94)	4.73 (4.49–4.91)
Oleic acid	Unsaturated fatty acids	7.25 (7.1–7.55)	7.21 (7.07–7.4)	7.63 (7.66–7.77)	7.73 (7.67–7.78)	7.7 (7.65–7.75)	7.7 (7.63–7.76)
Palmitelaidic acid	Unsaturated fatty acids	6.58 (6.27–6.82)	6.43 (6.04–6.82)	6.78 (6.76–7.03)	6.88 (6.76–6.98)	6.91 (6.81–7.01)	6.9 (6.79–7.01)

Supplementary Table 3. Reproducibility of quality control samples in metabolites.

Name	Classification	CV
Dodecane	Alkane	21.5
Nonacosane	Alkane	94.7
Tricosane	Alkane	29.6
Tridecane	Alkane	15.9
Decane, 2-methyl (NIST: 64.4%)	Alkane	24.2
Octadecane (NIST: 84.5%)	Alkane	37.0
beta-Alanine	Amino acid derivatives	20.2
beta-Citryl-L-glutamic acid	Amino acid derivatives	75.0
cis-4-Hydroxyproline	Amino acid derivatives	14.2
D_Norvaline	Amino acid derivatives	60.5
D_Proline	Amino acid derivatives	73.6
EDTA	Amino acid derivatives	21.2
Norleucine	Amino acid derivatives	38.9
Norvaline	Amino acid derivatives	17.2
Pyroglutamic acid	Amino acid derivatives	22.6
S-Adenosylmethionine	Amino acid derivatives	35.0
l-Proline, N-methoxycarbonyl-, octyl ester (NIST: 77.3%)	Amino acid derivatives	41.5
l-Prolylglycine, N-methoxycarbonyl-, methyl ester (NIST: 85.7%)	Amino acid derivatives	34.2
d-Prolyl-d-proline, N-methoxycarbonyl-, methyl ester (NIST: 92.1%)	Amino acid derivatives	9.9
d-Proline, N-methoxycarbonyl-, pentyl ester (NIST: 88.5%)	Amino acid derivatives	10.6
l-Valine, N-methoxycarbonyl-, pentyl ester (NIST: 62.8%)	Amino acid derivatives	11.9
l-Isoleucine, N-methoxycarbonyl-, methyl ester (NIST: 91.1%)	Amino acid derivatives	12.5
l-Leucine, N-methoxycarbonyl-, pentyl ester (NIST: 66.6%)	Amino acid derivatives	29.9

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Name	Classification	CV
Glycine, N-ethyl-N-(2-methoxyethoxycarbonyl)-, 2-methoxyethyl ester (NIST: 97.5%)	Amino acid derivatives	22.5
Alanine	Amino acids	13.1
Asparagine	Amino acids	17.8
Aspartic acid	Amino acids	9.3
Creatinine	Amino acids	23.8
Cysteine	Amino acids	21.1
Glutamic acid	Amino acids	12.5
Glutamine	Amino acids	17.3
Glutathione	Amino acids	15.4
Glycine	Amino acids	14.6
Histidine	Amino acids	10.5
Isoleucine	Amino acids	12.1
Leucine	Amino acids	12.5
Lysine	Amino acids	9.3
Methionine	Amino acids	21.5
Ornithine	Amino acids	13.2
Phenylalanine	Amino acids	12.0
Proline	Amino acids	10.6
Serine	Amino acids	15.2
Threonine	Amino acids	14.7
Tryptophan	Amino acids	27.3
Tyrosine	Amino acids	10.0
Valine	Amino acids	11.9
NADP_NADPH	Cofactors and Vitamins	21.0
Nicotinamide	Cofactors and Vitamins	50.2
Nicotinic acid	Cofactors and Vitamins	26.5
2-Phosphoenolpyruvic acid	Glycolytic intermediates	25.3
3-Methyl-2-oxovaleric acid	Keto acids and derivatives	61.2
Oxaloacetic acid	Keto acids and derivatives	35.7
Pyruvic acid	Keto acids and derivatives	30.7
Dimethyl aminomalonic acid	Organic acids	38.6
O-Acetylmalic anhydride	Organic acids	81.5
1-Aminocyclopropane-1-carboxylic acid	Organic acids	18.6
2-Aminobutyric acid	Organic acids	11.3
2-Hydroxybutyric acid	Organic acids	15.1
2-Hydroxyglutaramic acid	Organic acids	44.5

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Name	Classification	CV
2-Hydroxyisobutyric acid	Organic acids	29.9
2-Oxoadipic acid	Organic acids	31.3
2-Oxovaleric acid	Organic acids	33.7
3-Acetoxy-3-Hydroxy-2-methylpropionic acid (NIST: 88.6%)	Organic acids	44.7
4 Hydroxybenzene sulphonic acid	Organic acids	45.1
4-Aminobutyric acid (GABA)	Organic acids	21.5
4-Hydroxyphenylacetic acid	Organic acids	19.1
Azelaic acid	Organic acids	11.0
Benzoic acid	Organic acids	42.4
Cabamic acid	Organic acids	28.4
Caffeine	Organic acids	14.7
D_Indole-3-butyric acid	Organic acids	15.7
DBP	Organic acids	24.0
Dehydroabietic acid	Organic acids	63.5
Dehydroascorbic acid	Organic acids	19.4
Dipicolinic acid	Organic acids	17.5
Glutaric acid	Organic acids	32.5
Glyceric acid	Organic acids	21.8
Glyoxylic acid	Organic acids	33.1
Hippuric acid	Organic acids	19.0
Hydroxybenzoic acid	Organic acids	17.4
Lactic acid	Organic acids	14.8
Levulinic acid	Organic acids	25.6
Malonic acid	Organic acids	22.8
Oxalic acid	Organic acids	52.7
Phenethyl acetate	Organic acids	30.3
Suberic acid	Organic acids	18.0
Methyl 2-ethoxyacetate (NIST: 64.4%)	Organic acids	24.1
Paraldehyde (NIST: 69.9%)	Organic acids	41.5
Cyclopentane, hexyl- (NIST: 65.9%)	Organic acids	61.6
Oxetane, 2,3,4-trimethyl-, (2α,3a,4β)- (NIST: 64.2%)	Organic acids	20.7
2-Acetonyl-9-[3-deoxy-β-d-ribouranosyl]hypoxanthine (NIST: 67.8%)	Organic acids	65.0
Heptacosane (NIST: 78.9%)	Organic acids	30.3
Cycloheptasiloxane, tetradecamethyl- (NIST: 94.2%)	Organic acids	42.5
Cyclononasiloxane, octadecamethyl- (NIST: 91.7%)	Organic acids	58.1
2-Piperidinecarboxylic acid, 1-acetyl-, ethyl ester (NIST: 69.6%)	Organic acids	22.0

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Name	Classification	CV
4,4-Dimethyl-5-methylene[1,3]dioxolan-2-one (NIST: 60.5%)	Organic acids	20.2
3-Hydroxy-azetidine-1-carboxylic acid, methyl ester (NIST: 65.9%)	Organic acids	25.8
Methyl 2-methylhexanoate (NIST: 70.4%)	Organic acids	82.9
Benzeneacetic acid, methyl ester (NIST: 88.3%)	Organic acids	60.2
3-Furancarboxylic acid, methyl ester (NIST: 91.8%)	Organic acids	24.6
Furyl hydroxymethyl ketone (NIST: 88.1%)	Organic acids	46.0
Propanedioic acid, methyl,ethyl ester (NIST: 64%)	Organic acids	21.4
Acetophenone (NIST: 96.2%)	Organic acids	42.1
4-Pyridinecarboxaldehyde (NIST: 83.6%)	Organic acids	43.3
3-Pyridinecarboxaldehyde (NIST: 90.7%)	Organic acids	27.0
3H-Pyrazol-3-one, 2,4-dihydro-2,5-dimethyl- (NIST: 67.2%)	Organic acids	41.3
Butanedioyl dihydrazide (NIST: 70.6%)	Organic acids	15.7
2-Methoxy-N-(2-methoxy-propyl)-N-methyl-propionamide (NIST: 49.9%)	Organic acids	38.1
Dimethyl ethylidenemalonate (NIST: 80.4%)	Organic acids	27.6
2-Oxomalonic acid, methylhydrazone, dimethyl ester (NIST: 62%)	Organic acids	21.5
2,3-Furandione, dihydro-4,4-dimethyl (NIST: 91.3%)	Organic acids	46.4
2-(1-Pentamethylphenyl)ethyl-3,3-diphenyloxaziridine (NIST: 67.9%)	Organic acids	15.4
3,4-Methylenedioxyphenylacetic acid (NIST: 78.4%)	Organic acids	21.1
Bis(2-ethylhexyl) phthalate (NIST: 96.3%)	Organic acids	62.2
N-Ethylpyrrolidine-2,2-dicarboxilyc acid, dimethyl ester (NIST: 62.2%)	Organic acids	15.8
2-(4-(2-Acetoxyethyl)-2,5-dimethoxyphenyl)acetic acid, methyl ester (NIST: 63%)	Organic acids	21.3
BHT (Antioxidant)	Organic acids	39.1
Putrescine	Organic acids	10.6
1-(2-Methoxyethoxy)-2-methyl-2-propanol, methyl ether (NIST: 63.2%)	Organic acids	17.0
N(1-Methoxycarbonyl-1-methyl)ethyl-2-aza-1,3-dioxane (NIST: 87.4%)	Organic acids	23.3
Stearic acid (C18_0)	Saturated fatty acids	13.6
2-Methyloctadecanoic acid	Saturated fatty acids	46.3
3-Hydroxydecanoic acid	Saturated fatty acids	14.3
Adipic acid	Saturated fatty acids	27.9
Adrenic acid (C22_4n-6,9,12,15c)	Saturated fatty acids	32.4
Arachidic acid (C20_0)	Saturated fatty acids	31.1
Behenic acid (C22_0)	Saturated fatty acids	42.3
Decanoic acid (C10_0)	Saturated fatty acids	25.6
Dodecanoic acid (C12_0)	Saturated fatty acids	17.0
Hexanoic acid (C6_0)	Saturated fatty acids	45.8
Lignoceric acid (C24_0)	Saturated fatty acids	65.2

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Name	Classification	CV
Margaric acid (C17_0)	Saturated fatty acids	23.3
Myristic acid (C14_0)	Saturated fatty acids	18.8
Nonadecanoic acid (C19_0)	Saturated fatty acids	29.1
Octanoic acid (C8_0)	Saturated fatty acids	43.3
Palmitic acid (C16_0)	Saturated fatty acids	10.0
Pentadecanoic acid (C15_0)	Saturated fatty acids	22.2
Pimelic acid	Saturated fatty acids	17.4
Tridecanoic acid (C13_0)	Saturated fatty acids	95.0
Undecanoic acid (C11_0)	Saturated fatty acids	22.9
Tetradecanoic acid, 12-methyl-, methyl ester (NIST: 80.2%)	Saturated fatty acids	18.8
Tridecanoic acid, 12-methyl-, methyl ester (NIST: 89.6%)	Saturated fatty acids	23.4
2-Oxoglutaric acid	TCA cycle intermediates	29.6
cis-Aconitic acid	TCA cycle intermediates	20.8
Citramalic acid	TCA cycle intermediates	28.5
Citric acid	TCA cycle intermediates	28.0
Fumaric acid	TCA cycle intermediates	16.8
Isocitric acid	TCA cycle intermediates	18.7
Malic acid	TCA cycle intermediates	43.7
Succinic acid	TCA cycle intermediates	15.7
10-Pentadecenoic a+A2: A134cid (C15_1n-5c)	Unsaturated fatty acids	38.3
11,14-Eicosadienoic (C20_2n-6,9c)	Unsaturated fatty acids	25.9
13,16-Docosadienoic acid (C22_2n-6,9c)	Unsaturated fatty acids	39.1
3-Hydroxyoctanoic acid	Unsaturated fatty acids	38.2
3-Methyl-2-oxopentanoic acid	Unsaturated fatty acids	20.4
4-Methyl-2-oxopentanoic acid	Unsaturated fatty acids	16.8
9-Heptadecenoic acid (C17_1n-8t)	Unsaturated fatty acids	34.7
alpha-Linolenic acid (C18_3n-3,6,9c)	Unsaturated fatty acids	87.6
Arachidonic acid (C20_4n-6,9,12,15c)	Unsaturated fatty acids	22.0
cis-Vaccenic acid (C18_1n-7c)	Unsaturated fatty acids	10.4
Conjugated linoleic acid (C18_2n-9,11c)	Unsaturated fatty acids	11.6
DHA (C22_6n-3,6,9,12,15,18c)	Unsaturated fatty acids	32.4
Erucic acid (C22_1n-9c)	Unsaturated fatty acids	35.5
gamma-Linolenic acid (C18_3n-6,9,12c)	Unsaturated fatty acids	52.9
Gondoic acid (C20_1n-9c)	Unsaturated fatty acids	26.6
Itaconic acid	Unsaturated fatty acids	24.5
Linolelaidic acid (C18_ 2n-9,12c)	Unsaturated fatty acids	62.1

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Name	Classification	CV
Myristoleic acid (C14_1n-5c)	Unsaturated fatty acids	18.8
Nervonic acid (C24_1n-9c)	Unsaturated fatty acids	58.9
Oleic acid (C18_1n-9c)	Unsaturated fatty acids	10.4
Palmitelaidic acid (C16_1n-9c)	Unsaturated fatty acids	28.7
9,12-Octadecadienoic acid (Z,Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester (NIST: 83.7%)	Unsaturated fatty acids	25.9
14-Methylpentadec-9-enoic acid methyl ester (NIST: 70.8%)	Unsaturated fatty acids	12.0
But-2-enedioic acid, dimethyl ester (NIST: 86.5%)	Unsaturated fatty acids	17.5
(E,S)-2-Hexenoic acid, 4-amino-5-methyl-, methyl ester (NIST: 75.9%)	Unsaturated fatty acids	43.9
Butanedioic acid, ethyl methyl ester (NIST: 76.3%)	Unsaturated fatty acids	28.2
Butanedioic acid, dimethyl ester (NIST: 76.5%)	Unsaturated fatty acids	28.4

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