Electronic Supplementary Material (ESI) for Molecular BioSystems.

Supplementary materials:

KEGG-PATH: Kyoto encyclopedia of genes and genomes-based pathway analysis using a path analysis model

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Table S1 (a): The detailed impact data of KEGG pathway categories and subcategories from -15 to 300 vs. -30d in bovine mammary tissue during lactation; **(b)**: The detailed impact data of the secondary KEGG pathways from -15 to 300 vs. -30d in bovine mammary tissue during lactation.

Table S2 (a): The detailed impact direction data of KEGG pathway categories and subcategories from -15 to 300 vs. -30d in bovine mammary tissue during lactation; **(b):** The detailed impact direction data of the secondary KEGG pathways from -15 to 300 vs. -30d in bovine mammary tissue during lactation.

Table S3 (a): The subdivision of total effect between KEGG pathway categories and subcategories; **(b):** The subdivision of total effect between KEGG pathway subcategories and its secondary pathways.

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and “-” represent the up-regulating and down-regulating impact direction, respectively; **(b):** In the secondary KEGG pathways, the detailed comparisons between the total effect from KEGG-PATH approach and the average impact values from DIA method, and the impact direction results produced by the DIA method and the gradient analysis. The sign “+” and “-” represent the up-regulating and down-regulating impact direction, respectively.

S1: The pseudo-code of KEGG-PATH approach and the gradient analysis from principal component analysis in Matlab (R2008a, version 7.6.0.324).

.....The KEGG-PATH approach.....

```
Load X, Y;
function [BJ,Rxy,RBJ]=calcu(X,Y)
%BJ: direct effect; Rxy: the total effect; RBJ: the decomposed matrix, including direct and indirect effect.
X=X';
Y=Y';
[m,n]=size(X);
R=corrcoef(X);
Rxy=corr(X,Y);
BJ = linsolve(R,Rxy);      %BJ=R\Rxy; %BJ=inv(R)*Rxy;
RBJ=R.*repmat(BJ',size(R,1),1);
RBJ=RBJ';
abs(R*BJ-Rxy)./Rxy;
```

.....the gradient analysis from principal component analysis .....

```
X=X';
[m,n]=size(X);
R=corrcoef(X);
[P,Q]=eig(R);
eta = diag(Q)/n;
```

```
mainJ=0;
GS=zeros(n,1);
for i=1:length(eta)
    if sum(eta(1:i))>=0.99        %the accumulative variance contribution rate 0.99
        mainJ=i;
        break;
    end
end
GS=sum(P(:,1:mainJ),2);        %the impact direction from the gradient method
```

Table S1 (a) The detailed impact data of KEGG pathway categories and subcategories from -15 to 300 vs. -30d in bovine mammary tissue during lactation.

The categories and subcategories	Impact data							
	-15vs-30	1vs-30	15vs-30	30vs-30	60vs-30	120vs-30	240vs-30	360vs-30
1. Metabolism	23.2468	94.48154	118.0477	120.7041	184.0077	159.20106	59.611938	42.51941
1.1 Carbohydrate Metabolism	19.96829	114.7999	137.7713	130.3047	195.3783	175.22204	66.955242	40.25886
1.2 Energy Metabolism	21.32688	59.47765	90.62714	119.3132	89.37325	161.28881	67.237387	78.20142
1.3 Lipid Metabolism	31.95717	77.39551	93.41508	113.2328	195.8005	173.03834	58.885103	38.75722
1.4 Nucleotide Metabolism	14.5314	56.58635	63.72525	78.27943	95.1302	111.32539	42.900527	29.98792
1.5 Amino Acid Metabolism	20.3795	60.07464	81.12136	70.0212	107.0428	95.819597	39.655556	25.19765
1.6 Metabolism of Other Amino Acids	21.52776	50.00568	99.90674	62.16771	219.3925	157.88519	29.693727	29.51436
1.7 Glycan Biosynthesis and Metabolism	25.82043	77.12919	77.34517	93.84094	193.0432	156.4627	50.782029	33.61127
1.8 Metabolism of Cofactors and Vitamins	23.13116	96.36795	81.51642	112.8274	152.9149	137.10526	95.92608	90.81877
1.9 Metabolism of Terpenoids and Polyketides	87.32835	63.16768	109.4772	90.91175	93.96677	79.118383	87.328349	87.32835
1.10 Biosynthesis of Other Secondary Metabolites	741.8776	582.6431	874.2809	1515.113	778.0457	530.19149	170.99161	741.8776
1.11 Xenobiotics Biodegradation and Metabolism	18.29896	80.54072	115.9827	116.5002	168.4617	164.50032	73.052133	41.68891
2. Genetic Information Processing	29.01225	59.45205	45.5399	66.78752	104.2094	93.087316	28.197056	26.77298
2.1 Transcription	18.08969	35.95684	27.42328	44.71803	78.51178	74.964483	13.083188	11.93853
2.2 Translation	47.33266	57.32102	48.5645	73.91251	103.8245	104.92385	22.158949	27.90119
2.3 Folding, Sorting and Degradation	19.28328	61.81901	49.5252	66.31969	102.4447	99.692027	24.417172	24.92087
2.4 Replication and Repair	28.92013	70.21404	47.42818	72.43058	119.4377	82.877884	47.839345	35.10215
3. Environmental Information Processing	26.40572	92.29586	91.82688	110.8286	181.1549	148.58156	46.662407	40.41173
3.1 Membrane transport	33.57557	159.7749	163.7802	200.4142	334.5732	265.0118	42.149901	26.2671
3.2 Signal Transduction	25.16784	85.62687	82.07296	100.5379	164.2291	136.30249	37.780858	35.37252
3.3 Signaling Molecules and Interaction	28.55465	94.25584	103.6068	118.6991	192.0766	154.7947	80.732258	63.60374
4. Cellular Processes	21.00953	77.63061	78.0869	85.51778	147.9573	122.93389	47.182412	35.75154
4.1 Transport and Catabolism	23.81129	85.993	89.56679	94.8448	163.8031	115.98393	50.440697	38.21824

4.2 Cell Motility	17.58833	61.91513	48.14498	73.21768	139.2492	142.24465	46.69402	30.41049
4.3 Cell Growth and Death	21.28725	73.14617	81.78033	81.41566	135.3701	127.22432	40.269125	37.30837
4.4 Cell Communication	18.78536	75.59092	67.52907	81.03614	142.9142	122.50323	50.144941	32.4466
5. Organismal Systems	24.38492	91.86445	92.20447	100.0193	166.3564	145.78139	46.063706	39.86538
5.1 Immune System	24.49465	86.43688	78.55136	104.9152	177.1679	150.85335	37.914993	47.33609
5.2 Endocrine System	24.51365	125.6249	116.3495	122.4282	215.1971	170.22358	60.498675	47.93448
5.3 Circulatory System	17.60523	66.0782	63.41387	65.29133	101.289	107.14785	56.740204	27.20796
5.4 Digestive System	23.4884	88.25928	105.1363	90.06987	150.4517	135.47008	29.921965	30.83602
5.5 Excretory System	24.44551	103.007	125.4215	110.7031	168.2854	187.73929	87.337454	39.24459
5.6 Nervous System	28.45942	90.9831	79.40237	89.29623	148.4604	127.49941	25.893301	25.92762
5.7 Sensory System	27.92789	84.62284	81.24336	76.38106	134.1434	86.436673	57.290086	50.02818
5.8 Development	27.21408	93.31438	69.16293	97.16665	153.1451	131.63415	47.075955	41.36885
5.9 Environmental Adaptation	17.79245	5.438773	34.39059	50.38982	69.36291	33.800125	49.51526	13.5956

Table S1 (b) The detailed impact data of the secondary KEGG pathways from -15 to 300 vs. -30d in bovine mammary tissue during lactation.

The secondary pathways	Impact data							
	-15vs-30	1vs-30	15vs-30	30vs-30	60vs-30	120vs-30	240vs-30	360vs-30
1.1 Carbohydrate Metabolism								
1.1.1 Amino sugar and nucleotide sugar metabolism	26.9060	69.4765	89.3322	54.5503	140.2661	89.4779	20.3573	24.9236
1.1.2 Ascorbate and aldarate metabolism	21.9739	176.1643	203.3990	192.8539	298.9705	372.0990	61.7833	42.7452
1.1.3 Butanoate metabolism	93.7057	46.4407	52.9789	126.2874	146.3357	113.8669	104.3005	65.7294
1.1.4 Citrate cycle (TCA cycle)	7.1266	189.7712	229.2936	216.4733	325.2716	251.6535	131.0995	53.1468
1.1.5 Fructose and mannose metabolism	50.2822	81.5737	50.2988	86.5485	140.7122	186.8261	37.0938	31.6168
1.1.6 Galactose metabolism	11.0368	391.4770	422.0623	468.1758	523.2899	473.0402	295.4641	188.8554
1.1.7 Glycolysis / Gluconeogenesis	25.8794	83.3094	129.2772	101.7406	147.6890	120.4361	52.2033	23.1576
1.1.8 Glyoxylate and dicarboxylate metabolism	13.5778	65.7010	74.5017	104.0300	136.1297	76.0904	31.0861	15.6430
1.1.9 Inositol phosphate metabolism	26.2418	91.9141	74.4412	109.2348	165.4638	126.7210	29.4018	18.7156
1.1.10 Pentose and glucuronate interconversions	9.2701	140.1078	151.5156	98.4626	207.2411	214.1192	50.3070	8.9096
1.1.11 Pentose phosphate pathway	20.1651	5.9499	27.6013	36.0809	40.7921	53.9947	21.6653	14.5613
1.1.12 Propanoate metabolism	11.9114	70.7992	99.9335	54.8943	133.6615	86.9227	11.8736	4.6330
1.1.13 Pyruvate metabolism	15.2483	105.0975	119.5039	92.5572	163.1985	164.8080	72.8726	30.7280
1.1.14 Starch and sucrose metabolism	95.5789	89.4158	94.4893	82.3761	166.2745	123.0528	17.8650	95.5789
1.2 Energy Metabolism								
1.2.1 Nitrogen metabolism	43.8307	31.6061	59.0652	34.9770	31.7148	90.8134	14.8075	43.8307
1.2.2 Oxidative phosphorylation	21.3269	76.3877	68.6093	87.3014	119.5630	109.9804	62.2181	45.0148
1.2.3 Sulfur metabolism	155.1852	70.4392	144.2069	235.6612	116.8420	283.0726	124.6865	111.3880
1.3 Lipid Metabolism								
1.3.1 alpha-Linolenic acid metabolism	28.5186	61.2689	41.1350	46.4497	74.0193	107.1214	53.8355	18.3359
1.3.2 Arachidonic acid metabolism	14.4152	111.2109	118.1798	116.6736	212.6504	175.4098	48.1946	25.1413
1.3.3 Biosynthesis of unsaturated fatty acids	223.7080	80.6848	216.7198	267.5952	512.7195	327.2014	92.3132	68.7220

1.3.4 Ether lipid metabolism	40.8089	111.2469	84.4701	127.8911	188.7185	224.6657	17.8522	31.1524
1.3.5 Fatty acid elongation in mitochondria	69.6170	67.5905	30.9040	68.0913	132.7653	96.8288	69.6170	21.5177
1.3.6 Fatty acid metabolism	18.1136	50.2395	96.7570	67.1697	107.5189	100.4283	43.6504	17.3100
1.3.7 Glycerolipid metabolism	36.9785	93.7213	135.2823	103.3889	165.7481	148.1917	24.8421	34.4469
1.3.8 Glycerophospholipid metabolism	33.4714	115.1371	99.3022	103.9636	171.5643	182.5214	18.3488	30.1337
1.3.9 Primary bile acid biosynthesis	78.0995	67.6622	117.5603	55.2504	92.0554	68.3562	67.7128	78.0995
1.3.10 Sphingolipid metabolism	20.6963	81.1785	56.6431	84.5635	175.6625	115.0584	24.5714	18.1385
1.3.11 Steroid biosynthesis	64.7697	39.5089	43.4318	123.4396	317.8431	267.7552	75.5452	35.7569
1.3.12 Steroid hormone biosynthesis	29.8424	61.4570	41.5635	68.1680	94.9814	172.8178	91.1685	18.5383
1.3.13 Synthesis and degradation of ketone bodies	215.0921	116.1019	132.4472	315.7186	318.8050	263.1423	143.5369	145.8930
1.4 Nucleotide Metabolism								
1.4.1 Purine metabolism	17.6391	65.8600	63.6524	90.6334	113.8672	124.0048	35.8439	25.9469
1.4.2 Pyrimidine metabolism	11.4237	47.3127	63.7981	65.9254	76.3932	98.6460	49.9572	34.0290
1.5 Amino Acid Metabolism								
1.5.1 Alanine, aspartate and glutamate metabolism	23.4388	12.6537	4.8671	22.9820	50.9417	51.3627	7.9287	13.3354
1.5.2 Arginine and proline metabolism	23.6452	57.9717	93.8652	35.5673	96.4437	104.7469	18.4524	40.5592
1.5.3 Cysteine and methionine metabolism	29.8774	86.6240	106.2392	98.5703	166.9007	76.2306	6.3864	50.8050
1.5.4 Glycine, serine and threonine metabolism	46.1465	108.3850	84.3677	123.1083	175.1503	122.3504	46.4633	8.2332
1.5.5 Histidine metabolism	16.8657	91.2309	142.9207	75.8598	145.4578	121.5551	60.2389	20.8080
1.5.6 Lysine degradation	16.2117	52.1313	72.4962	47.9850	77.8000	99.9481	5.2161	4.4548
1.5.7 Phenylalanine metabolism	7.5853	30.4168	39.4983	22.1778	34.1763	16.5222	53.4030	12.2009
1.5.8 Tryptophan metabolism	14.1366	53.7261	116.7897	84.6026	103.5023	115.6496	53.0386	34.7235
1.5.9 Tyrosine metabolism	3.3375	20.4048	63.1145	59.0567	55.4660	54.1032	65.7857	28.9491
1.5.10 Valine, leucine and isoleucine biosynthesis	42.4448	69.4101	70.4185	80.6714	99.9301	117.1949	35.7237	14.0826
1.5.11 Valine, leucine and isoleucine degradation	3.5445	77.8665	97.7578	119.6519	171.7017	174.3520	83.5743	49.0226
1.6 Metabolism of Other Amino Acids								

1.6.1 beta-Alanine metabolism	22.6371	80.3223	130.2861	68.0544	127.6577	109.2301	26.0512	15.6060
1.6.2 Glutathione metabolism	14.5246	80.0546	129.3435	111.1736	245.9588	210.4024	65.0250	44.2540
1.6.3 Selenoamino acid metabolism	27.4215	30.7818	40.0906	52.8407	79.3347	115.0572	9.7293	12.7556
1.6.4 Taurine and hypotaurine metabolism	101.4887	8.8640	101.4887	39.3850	322.0057	177.3681	23.8315	37.4781
1.7 Glycan Biosynthesis and Metabolism								
1.7.1 Glycosaminoglycan biosynthesis - chondroitin sulfate	9.4122	72.2388	85.0559	141.8019	159.1559	147.8461	43.5871	72.2111
1.7.2 Glycosaminoglycan biosynthesis - heparan sulfate	43.6410	107.5242	142.5142	114.2502	206.6867	134.3602	57.3024	17.7534
1.7.3 Glycosaminoglycan biosynthesis - keratan sulfate	22.8524	60.7851	27.0418	41.9465	124.9063	87.5011	12.6555	53.9555
1.7.4 Glycosaminoglycan degradation	21.0600	41.1341	62.8858	57.9455	174.8100	99.1995	26.4538	43.8206
1.7.5 Glycosphingolipid biosynthesis - ganglio series	37.0625	59.1026	32.8944	67.2412	241.1030	186.6271	91.0184	13.0979
1.7.6 Glycosphingolipid biosynthesis - globo series	31.4145	52.6909	74.6927	30.1719	178.1122	138.2763	74.6927	17.4905
1.7.7 Glycosphingolipid biosynthesis - lacto and neolacto series	13.4209	46.6591	63.4708	94.7322	167.4117	127.5048	43.8433	17.4975
1.7.8 Glycosylphosphatidylinositol(GPI)-anchor biosynthesis	51.4439	308.9391	304.8119	378.9596	500.6690	574.6078	183.5872	128.0869
1.7.9 N-Glycan biosynthesis	4.4321	40.8912	57.2144	49.8920	134.3252	74.7628	22.7755	5.9178
1.7.10 O-Glycan biosynthesis	27.8257	55.6195	17.2034	18.2882	109.9630	104.7369	55.6061	55.6061
1.7.11 O-Mannosyl glycan biosynthesis	32.4967	62.6013	45.0328	71.4278	146.9280	160.5152	16.0515	7.1390
1.7.12 Other glycan degradation	14.7832	17.3645	12.6714	59.4342	172.4470	41.6145	47.3447	13.0979
1.8 Metabolism of Cofactors and Vitamins								
1.8.1 Folate biosynthesis	37.6768	5.7442	34.9864	48.6006	125.4923	47.7765	64.9525	154.3905
1.8.2 Nicotinate and nicotinamide metabolism	23.7507	16.1997	56.0796	77.8782	89.3385	120.3910	73.7542	71.9073
1.8.3 One carbon pool by folate	56.5752	28.0662	35.7230	16.5895	125.0755	27.4759	56.5752	106.5212
1.8.4 Pantothenate and CoA biosynthesis	21.1915	60.8105	82.7242	63.6235	141.0032	145.3938	90.3037	26.6981
1.8.5 Porphyrin and chlorophyll metabolism	13.5862	57.0886	89.6570	105.6008	206.1338	163.9219	45.1369	97.3036
1.8.6 Retinol metabolism	11.5080	75.3724	101.4299	136.7913	215.4281	164.4104	44.7190	14.0573
1.8.7 Riboflavin metabolism	107.4750	132.0313	157.6801	137.4212	89.9684	123.6561	37.5558	74.0122
1.8.8 Vitamin B6 metabolism	198.9522	198.9522	93.8513	146.1947	192.3943	246.5385	284.0869	230.6476

1.11 Xenobiotics Biodegradation and Metabolism								
1.11.1 Drug metabolism - cytochrome P450	21.5919	45.0957	88.6152	96.7815	129.6492	142.6659	108.8997	74.8921
1.11.2 Drug metabolism - other enzymes	9.0142	151.1406	183.2348	173.9012	250.5637	210.4131	41.8223	28.8465
1.11.3 Metabolism of xenobiotics by cytochrome P450	24.2908	45.3859	76.0981	78.8178	125.1721	140.4219	68.4345	21.3281
2.1 Transcription								
2.1.1 Basal transcription factors	27.6247	13.6710	19.8353	34.9367	62.4781	56.1516	10.8713	16.1225
2.1.2 RNA polymerase	18.6325	50.6165	35.0510	51.5730	85.2643	68.2125	22.2699	7.0090
2.1.3 Spliceosome	8.0118	43.5830	27.3835	47.6443	87.7930	100.5293	6.1084	12.6841
2.2 Translation								
2.2.1 Aminoacyl-tRNA biosynthesis	29.9700	88.2182	90.9813	71.8975	85.4941	95.2067	29.1410	20.1142
2.2.2 mRNA surveillance pathway	5.5786	92.2371	63.9552	110.8202	157.8990	150.8313	20.5008	26.0601
2.2.3 Ribosome	146.4002	14.7469	21.1503	65.6618	123.7840	95.1985	33.2958	29.3736
2.2.4 Ribosome biogenesis in eukaryotes	28.7883	44.5355	28.5171	58.6097	79.3972	90.4277	2.6080	14.8726
2.2.5 RNA transport	25.9263	46.8674	38.2185	62.5733	72.5484	92.9551	25.2491	49.0855
2.3 Folding, Sorting and Degradation								
2.3.1 Proteasome	23.0468	34.5102	18.1886	23.8841	44.5052	77.9248	8.8279	34.5815
2.3.2 Protein export	86.6874	124.4562	96.2146	81.6850	125.6816	81.5519	86.6874	10.5349
2.3.3 Protein processing in endoplasmic reticulum	10.0443	72.3292	62.6196	70.3863	131.8188	108.8753	39.1677	38.4607
2.3.4 RNA degradation	19.5734	50.2250	29.5821	60.8702	66.8910	101.8864	30.8860	12.2964
2.3.5 SNARE interactions in vesicular transport	29.3199	69.3502	36.0728	55.4254	77.3043	93.1490	24.7521	39.2650
2.3.6 Sulfur relay system	17.0479	27.2995	49.1947	116.6933	168.6621	132.1567	26.3758	76.7757
2.3.7 Ubiquitin mediated proteolysis	16.6673	54.5628	54.8040	55.2935	102.2496	102.3000	16.4936	14.3867
2.4 Replication and Repair								
2.4.1 Base excision repair	31.3711	59.8128	30.8209	59.4510	62.8045	65.9173	32.9073	36.1362
2.4.2 DNA replication	26.9354	76.5538	81.0965	82.7432	129.0976	109.4388	53.5854	46.6473
2.4.3 Homologous recombination	28.3723	97.2052	53.4809	126.9121	193.7701	111.4630	67.7248	41.6450

2.4.4 Mismatch repair	29.2393	54.0388	39.0646	64.0497	66.9435	60.5363	53.1814	27.3978
2.4.5 Non-homologous end-joining	69.2157	77.5233	28.4587	30.0641	171.2605	69.2157	69.2457	38.7717
2.4.6 Nucleotide excision repair	28.6826	56.1503	51.6476	71.3636	92.7501	67.0341	31.7979	20.0149
3.2 Signal Transduction								
3.2.1 Calcium signaling pathway	25.5126	93.9573	76.0648	100.0995	164.4149	138.8999	23.6263	40.4765
3.2.2 ErbB signaling pathway	25.3924	67.8284	67.3226	96.4518	145.4202	123.5051	18.3874	19.6126
3.2.3 Hedgehog signaling pathway	30.9789	114.3446	148.5749	148.2467	242.3200	226.3042	77.2848	73.3020
3.2.4 Jak-STAT signaling pathway	35.5817	104.8894	105.6662	135.9511	219.8974	167.1842	33.2314	25.5261
3.2.5 MAPK signaling pathway	27.7524	72.6248	74.1726	76.9998	144.0190	121.3675	28.6858	29.4547
3.2.6 mTOR signaling pathway	18.5354	64.6309	35.1797	64.3780	113.6250	64.3443	14.7034	13.8524
3.2.7 Notch signaling pathway	5.1553	78.8513	76.6708	103.9239	150.6173	109.1004	30.6749	33.8424
3.2.8 Phosphatidylinositol signaling system	19.9984	67.7473	61.2203	67.7841	145.6030	111.3295	30.1282	23.6978
3.2.9 TGF-beta signaling pathway	8.7429	101.9256	130.6590	135.4736	206.1994	149.7195	96.6673	50.8218
3.2.10 VEGF signaling pathway	48.2942	98.8465	63.9527	91.3426	139.5489	152.3452	26.6449	41.5367
3.2.11 Wnt signaling pathway	30.9020	76.2493	63.3190	85.2659	134.8547	135.2275	35.5549	36.9746
3.3 Signaling Molecules and Interaction								
3.3.1 Cell adhesion molecules (CAMs)	22.3712	103.0364	102.0923	125.8492	204.7468	191.9790	72.8725	77.7004
3.3.2 Cytokine-cytokine receptor interaction	38.6756	91.6168	94.6775	106.9919	161.0110	139.2949	49.0060	42.7731
3.3.3 ECM-receptor interaction	24.6171	88.1144	114.0506	123.2561	210.4720	133.1103	120.3182	70.3378
3.3.4 Neuroactive ligand-receptor interaction	24.9246	119.1127	115.9640	212.4793	347.9441	327.9763	93.4834	123.9742
4.1 Transport and Catabolism								
4.1.1 Endocytosis	22.5098	49.7486	58.9954	59.1782	117.4333	88.5926	41.1411	29.0780
4.1.2 Lysosome	20.4253	59.3815	49.9510	66.8025	129.9858	97.3483	36.6775	37.1362
4.1.3 Peroxisome	32.9660	108.6937	138.5018	135.2491	232.5274	170.5600	58.9020	46.8933
4.1.4 Phagosome	19.3441	107.6980	108.3229	131.0068	196.7680	184.5880	103.2921	72.5338
4.1.5 Regulation of autophagy	68.1809	104.4431	92.0629	81.9873	142.3012	38.8308	12.1907	5.4499

4.3 Cell Growth and Death								
4.3.1 Apoptosis	24.7850	56.6594	55.8005	65.0792	125.9284	112.5841	41.4237	33.9571
4.3.2 Cell cycle	13.5036	86.7704	88.6280	88.3041	135.0274	126.0311	36.8813	37.6037
4.3.3 Oocyte meiosis	15.6111	79.3127	68.9021	91.5868	140.6267	112.6886	26.0484	26.9444
4.3.4 p53 signaling pathway	31.2494	69.8421	113.7907	80.6926	139.8981	157.5936	56.7231	50.7283
4.4 Cell Communication								
4.4.1 Adherens junction	14.7221	51.1057	42.7151	57.5265	87.1063	81.5489	44.6887	23.2475
4.4.2 Focal adhesion	17.3666	61.2405	63.7557	77.7385	144.0062	121.1237	65.3078	37.0423
4.4.3 Gap junction	25.2270	94.8339	72.0472	93.0751	165.8898	144.0317	45.0338	22.5329
4.4.4 Tight junction	17.8257	95.1835	91.5983	95.8045	174.6544	143.3086	45.5495	46.9637
5.1 Immune System								
5.1.1 Antigen processing and presentation	24.9246	119.1127	115.9640	212.4793	347.9441	327.9763	93.4834	123.9742
5.1.2 B cell receptor signaling pathway	26.4566	74.0560	63.5314	78.8397	153.9693	128.1762	43.5977	34.9818
5.1.3 Chemokine signaling pathway	20.2963	82.2162	73.4752	87.6151	139.1736	127.5344	37.4401	42.9790
5.1.4 Complement and coagulation cascades	7.1384	81.7695	117.6822	133.9028	179.5708	146.6077	55.1171	59.9689
5.1.5 Cytosolic DNA-sensing pathway	36.7138	40.1017	47.1312	44.9932	112.2147	68.7512	3.4967	19.9231
5.1.6 Fc epsilon RI signaling pathway	19.3481	103.3176	86.3545	139.1239	249.5420	193.4499	45.7887	49.3701
5.1.7 Fc gamma R-mediated phagocytosis	13.2291	79.9740	59.7775	95.8548	169.3161	157.7590	47.3323	37.8674
5.1.8 Hematopoietic cell lineage	35.2650	125.9446	133.5587	135.5418	221.5530	165.1029	46.6374	72.4061
5.1.9 Intestinal immune network for IgA production	24.7061	105.2775	96.5048	120.4796	191.2465	172.2098	35.8436	53.8181
5.1.10 Leukocyte transendothelial migration	13.5869	72.5502	64.8354	72.8391	136.9136	128.4893	33.8666	39.5842
5.1.11 Natural killer cell mediated cytotoxicity	24.4738	102.6260	82.8547	120.1266	165.9205	172.5044	29.1594	43.6724
5.1.12 NOD-like receptor signaling pathway	20.8794	81.9792	59.6835	90.5166	146.6598	139.6451	17.3259	28.2089
5.1.13 RIG-I-like receptor signaling pathway	35.7352	72.9792	52.9821	68.1060	166.9535	97.4729	21.2056	32.1585
5.1.14 T cell receptor signaling pathway	34.6984	76.3181	58.1454	80.3669	138.3962	115.8473	27.6688	29.6781
5.1.15 Toll-like receptor signaling pathway	29.9681	78.3307	65.7896	92.9432	138.1441	121.2739	30.7618	41.4507

5.2 Endocrine System								
5.2.1 Adipocytokine signaling pathway	30.4134	137.8819	153.4261	144.2353	244.2621	192.5327	72.3407	45.8904
5.2.2 GnRH signaling pathway	27.9087	122.4916	92.9678	122.1599	216.8166	166.0279	26.7129	29.2052
5.2.3 Insulin signaling pathway	19.4422	77.0145	61.4148	74.2447	136.6769	120.8497	42.0164	33.5119
5.2.4 Melanogenesis	33.9943	88.9745	49.5073	83.4333	129.7480	138.7395	28.7844	26.8935
5.2.5 PPAR signaling pathway	22.0233	257.8563	355.2313	312.6265	433.3840	368.0951	161.2477	126.6981
5.2.6 Renin-angiotensin system	13.2999	69.5303	55.8454	78.7198	135.4942	114.6632	31.8898	25.4077
5.3 Circulatory System								
5.3.1 Cardiac muscle contraction	9.7679	55.0501	60.1010	53.9839	90.7023	98.8524	78.3310	27.7165
5.3.1 Vascular smooth muscle contraction	25.4425	77.1063	66.7268	76.5988	111.8758	115.4433	35.1494	26.6994
5.4 Digestive System								
5.4.1 Bile secretion	46.7982	127.5758	135.7992	134.3431	212.1350	201.1753	40.3591	15.7304
5.4.2 Carbohydrate digestion and absorption	6.1399	58.7890	103.9118	60.9106	85.7570	84.4818	6.2881	58.0398
5.4.3 Fat digestion and absorption	21.2833	125.8631	117.4985	100.3651	199.0327	182.6429	38.0233	43.1205
5.4.4 Gastric acid secretion	19.2825	91.7550	82.0455	83.3381	149.8280	155.2970	19.7018	22.2308
5.4.5 Mineral absorption	29.8183	53.4733	92.6053	72.7387	104.3349	98.5519	49.7342	18.1891
5.4.6 Pancreatic secretion	41.3669	88.7042	101.0493	85.8202	165.7897	162.1501	21.3276	25.2635
5.4.7 Protein digestion and absorption	6.4086	72.0141	143.2536	88.4057	126.0439	100.3847	47.6758	61.3188
5.4.8 Salivary secretion	21.4685	115.2198	119.7488	109.8644	200.2214	179.6704	16.2658	29.9990
5.4.9 Vitamin digestion and absorption	18.8295	60.9393	50.3143	74.8430	110.9225	54.8765	61.7875	61.7875
5.5 Excretory System								
5.5.1 Aldosterone-regulated sodium reabsorption	14.2778	78.1081	105.2802	78.1513	154.3094	158.7702	3.4739	6.3419
5.5.2 Collecting duct acid secretion	25.6534	108.1045	91.8192	125.6651	154.2024	130.6536	102.7965	70.7198
5.5.3 Endocrine and other factor-regulated calcium reabsorption	37.7918	98.3413	128.8146	110.3328	163.0553	190.1646	59.1739	27.6770
5.5.4 Proximal tubule bicarbonate reclamation	32.7189	194.4290	277.0443	204.6749	322.9102	401.5919	226.5285	67.8257

5.5.5 Vasopressin-regulated water reabsorption	11.7856	36.0524	24.1490	34.6915	46.9498	57.5161	44.7145	23.6586
5.6 Nervous System								
5.6.1 Glutamatergic synapse	25.5654	105.1728	89.9110	102.5245	160.1590	145.7472	18.0896	24.9511
5.6.2 Long-term depression	35.3774	87.4887	86.5246	95.8708	168.7396	141.5792	33.1305	24.1751
5.6.3 Long-term potentiation	33.7597	93.4093	79.8990	85.9348	145.9800	128.7391	28.7175	30.0028
5.6.4 Neurotrophin signaling pathway	19.1353	77.8615	61.2749	72.8549	118.9629	93.9321	23.6357	24.5815
5.8 Development								
5.8.1 Axon guidance	37.3980	116.9966	75.2288	105.8081	167.6733	164.9784	40.1506	52.5687
5.8.2 Dorso-ventral axis formation	99.3535	97.1541	63.2063	98.8841	143.8990	123.7430	69.2347	99.3535
5.8.3 Osteoclast differentiation	17.0302	65.7925	69.0536	86.8077	147.8630	106.1810	31.8426	30.1690

Table S2 (a) The detailed impact direction data of KEGG pathway categories and subcategories from -15 to 300 vs. -30d in bovine mammary tissue during lactation.

The categories and subcategories	Impact direction data							
	-15vs-30	1vs-30	15vs-30	30vs-30	60vs-30	120vs-30	240vs-30	360vs-30
1. Metabolism	9.999874	41.24521	54.61146	47.76903	73.89263	50.93272	12.25234	18.02546
1.1 Carbohydrate Metabolism	6.296173	29.93262	61.15663	29.56029	34.15944	11.87742	8.967086	17.16677
1.2 Energy Metabolism	19.09275	35.74512	12.05708	-45.3216	-2.83388	-25.0228	-47.2464	23.3595
1.3 Lipid Metabolism	18.58993	24.09033	33.25744	48.9813	104.0971	73.42268	23.80128	27.14268
1.4 Nucleotide Metabolism	10.37536	7.773943	-7.04111	0.599144	8.696862	-15.0124	-24.6647	-21.4995
1.5 Amino Acid Metabolism	8.56564	9.641917	19.68514	6.711381	13.63608	25.98636	-7.8858	16.25941
1.6 Metabolism of Other Amino Acids	10.79533	31.99126	50.3428	39.73279	181.4706	105.3019	13.94075	24.9331
1.7 Glycan Biosynthesis and Metabolism	8.925333	20.65338	28.26552	24.46785	56.62789	54.36586	10.88833	15.04207
1.8 Metabolism of Cofactors and Vitamins	10.41035	57.02909	20.29483	59.44407	36.89277	34.41934	37.96522	15.1199
1.9 Metabolism of Terpenoids and Polyketides	64.38563	25.45539	77.36729	46.02032	93.96677	79.11838	64.38563	64.38563
1.10 Biosynthesis of Other Secondary Metabolites	737.5859	582.6431	874.2809	1515.113	778.0457	504.4412	170.9916	737.5859
1.11 Xenobiotics Biodegradation and Metabolism	2.892415	11.29431	-18.8633	-12.4496	6.533286	-8.21603	43.16212	22.4579
2. Genetic Information Processing	20.29306	-6.30529	-0.87349	-21.9059	-10.1989	-22.5758	-14.766	-2.95794
2.1 Transcription	14.68802	17.1939	13.40303	3.915299	15.95192	5.058035	10.99436	10.98476
2.2 Translation	38.64885	-4.84927	5.913576	-24.3365	-29.8991	-51.7087	-17.0217	-8.74099
2.3 Folding, Sorting and Degradation	11.723	15.91462	16.59391	-12.6626	-7.29654	-27.9743	-2.25776	8.628453
2.4 Replication and Repair	15.58437	-45.1915	-34.0463	-43.5749	-10.2434	-2.46525	-42.9766	-16.6965
3. Environmental Information Processing	10.39221	19.37459	26.98187	13.66904	27.36128	16.59064	16.26437	6.838724
3.1 Membrane transport	-9.94851	38.88183	87.27707	46.28982	30.71713	23.61256	28.31806	-26.2671
3.2 Signal Transduction	11.03972	18.67005	24.5136	12.16815	29.81295	16.37864	10.73717	7.574856
3.3 Signaling Molecules and Interaction	14.79828	15.4555	15.93377	8.298711	17.25323	15.02733	32.51288	15.17485
4. Cellular Processes	3.068721	4.256864	12.79934	0.08929	4.924231	-10.7081	11.93127	0.388143
4.1 Transport and Catabolism	3.151166	18.14775	26.90217	11.2176	13.37936	-7.96536	9.959735	-0.5105

4.2 Cell Motility	-0.93941	0.447307	6.699079	-9.58193	-22.726	-28.9825	25.00676	2.24645
4.3 Cell Growth and Death	3.857628	-11.1011	-6.00371	-13.7442	-2.08296	-16.4087	0.110605	-0.6008
4.4 Cell Communication	3.199404	3.203631	15.49891	2.430234	8.27507	-3.8675	22.94748	2.035812
5. Organismal Systems	8.275885	8.440833	28.94972	8.288143	25.76815	3.154405	1.953118	1.458203
5.1 Immune System	19.40324	23.56681	30.02626	22.86666	38.3768	17.50042	9.393527	1.974745
5.2 Endocrine System	6.047058	30.25406	35.71797	24.38631	55.64418	26.35558	-6.69855	5.831286
5.3 Circulatory System	6.187855	-0.22913	17.15127	-5.44606	17.36679	10.60626	0.809708	3.275651
5.4 Digestive System	3.05509	-0.02623	36.20945	1.437199	18.99405	0.491896	-1.0704	6.326125
5.5 Excretory System	-4.65411	-42.4147	23.68845	-33.8489	-17.5238	-64.9109	-17.7489	-9.77958
5.6 Nervous System	7.385258	9.58292	16.40343	8.366998	15.32824	11.32984	4.40456	4.102983
5.7 Sensory System	-2.97966	-0.02309	19.46563	-18.4093	4.568151	-44.4727	-41.1002	-34.7248
5.8 Development	9.857014	11.0499	20.70585	14.86876	20.77705	11.04331	31.29674	14.03301
5.9 Environmental Adaptation	-17.7925	-5.43877	34.39059	-16.6246	-0.33147	-33.8001	12.45872	-13.5956

Table S2 (b) The detailed impact direction data of the secondary KEGG pathways from -15 to 300 vs. -30d in bovine mammary tissue during lactation.

The secondary pathways	Impact direction data							
	-15vs-30	1vs-30	15vs-30	30vs-30	60vs-30	120vs-30	240vs-30	360vs-30
1.1 Carbohydrate Metabolism								
1.1.1 Amino sugar and nucleotide sugar metabolism	14.86587	49.31663	60.72345	24.32683	26.078602	10.080432	4.9903123	24.923593
1.1.2 Ascorbate and aldarate metabolism	2.128408	-7.27952	108.3427	-28.9609	-70.53701	-149.8174	-34.65962	-19.5803
1.1.3 Butanoate metabolism	65.48596	23.81337	33.71297	73.22402	86.320549	71.300967	104.30046	65.729401
1.1.4 Citrate cycle (TCA cycle)	7.126608	84.57155	134.9676	122.998	194.37232	64.158378	-30.01656	-6.539864
1.1.5 Fructose and mannose metabolism	30.99687	-22.8747	1.136213	-22.4678	5.5371609	26.543294	12.311848	18.126206
1.1.6 Galactose metabolism	-11.0368	334.5009	361.5297	366.0755	402.31534	384.79107	252.07253	188.85535
1.1.7 Glycolysis / Gluconeogenesis	17.63415	-29.3335	-22.801	-53.138	-49.93834	-26.78742	-27.52649	-11.5439
1.1.8 Glyoxylate and dicarboxylate metabolism	-13.5778	-65.701	-74.5017	-56.7549	-60.60938	-41.10065	-31.08611	-15.643
1.1.9 Inositol phosphate metabolism	6.89226	35.90905	46.8414	26.04096	85.854533	54.351846	8.3354699	2.314181
1.1.10 Pentose and glucuronate interconversions	9.270129	80.36225	119.9423	49.18333	40.23379	-43.13333	-29.44259	8.9095596
1.1.11 Pentose phosphate pathway	20.16513	-5.94988	-8.25185	-2.60661	-40.79211	7.6471332	-21.66529	-14.56132
1.1.12 Propanoate metabolism	-2.27046	2.842604	24.76318	10.66295	-8.162775	11.867377	-1.02412	4.632971
1.1.13 Pyruvate metabolism	-6.64037	-39.3459	-8.16759	-34.024	-53.55828	-80.5651	-63.18561	-22.45484
1.1.14 Starch and sucrose metabolism	-48.9573	-21.7752	8.547157	-60.7154	-78.8822	-123.0528	-17.86502	-48.9573
1.2 Energy Metabolism								
1.2.1 Nitrogen metabolism	-0.64914	-1.44978	29.08035	-5.97973	-31.71479	20.976674	-14.80754	-0.64914
1.2.2 Oxidative phosphorylation	19.09275	38.24597	39.45105	31.76879	48.66488	41.923103	-2.245263	39.75717
1.2.3 Sulfur metabolism	-57.8314	70.43918	-32.3602	-161.754	-25.45173	-137.9681	-124.6865	6.9618328
1.3 Lipid Metabolism								
1.3.1 alpha-Linolenic acid metabolism	28.51864	61.26886	41.13497	46.44969	74.019313	89.552256	51.32566	18.335884
1.3.2 Arachidonic acid metabolism	4.59725	73.13447	99.6524	80.59114	164.71253	140.50761	32.025103	25.141273
1.3.3 Biosynthesis of unsaturated fatty acids	163.2355	24.11094	130.8832	197.3313	397.71499	261.63032	62.255957	68.722012

1.3.4 Ether lipid metabolism	29.53174	81.96407	33.36462	46.97923	125.62965	114.10343	-6.415999	31.152444
1.3.5 Fatty acid elongation in mitochondria	-69.6163	-67.5905	-30.904	-68.0913	-132.7653	-96.82881	-69.6163	-21.5177
1.3.6 Fatty acid metabolism	6.040261	0.937722	-2.28987	-17.5052	-38.29665	-33.07027	0.8433563	2.7583458
1.3.7 Glycerolipid metabolism	28.99157	76.85226	119.2787	84.47249	113.775	93.309532	1.8788609	25.24514
1.3.8 Glycerophospholipid metabolism	14.00633	18.93994	27.34359	10.9703	57.53806	18.936986	-5.535567	2.5778022
1.3.9 Primary bile acid biosynthesis	-78.0996	-67.6622	-117.56	-55.2504	-92.05535	-68.35618	-67.71284	-78.0996
1.3.10 Sphingolipid metabolism	20.6963	64.19118	56.64309	84.56348	166.75329	115.05837	2.7593325	18.138482
1.3.11 Steroid biosynthesis	64.76965	23.70503	19.9879	123.4396	226.95559	230.14102	75.545246	0.7922877
1.3.12 Steroid hormone biosynthesis	-29.8424	-38.6493	-29.47	-68.168	-45.61171	-110.2668	22.633749	8.4731705
1.3.13 Synthesis and degradation of ketone bodies	154.1312	59.53343	84.28242	183.06	262.83547	199.77743	143.5369	145.89302
1.4 Nucleotide Metabolism								
1.4.1 Purine metabolism	11.82942	24.62952	25.31331	23.79653	29.196528	9.7976935	-13.33241	-13.36374
1.4.2 Pyrimidine metabolism	8.921302	-9.08163	-39.3955	-22.5982	-11.8028	-39.82256	-35.99695	-29.63526
1.5 Amino Acid Metabolism								
1.5.1 Alanine, aspartate and glutamate metabolism	-0.44779	-12.6537	-4.86708	0.703728	0.5614358	7.7143916	-7.928725	13.335432
1.5.2 Arginine and proline metabolism	23.64516	28.87851	39.21126	5.406	33.114487	64.318249	-11.67149	25.780267
1.5.3 Cysteine and methionine metabolism	4.982123	-55.3935	-58.6579	-45.14	-80.74938	-48.92663	-6.386358	28.068145
1.5.4 Glycine, serine and threonine metabolism	-3.25693	0.664394	-66.5565	-25.1934	0.9410113	7.3391707	-46.46331	-8.233157
1.5.5 Histidine metabolism	16.86566	68.09983	112.1292	55.14047	44.416762	61.637966	-17.63934	20.807962
1.5.6 Lysine degradation	6.522914	21.53624	61.38122	15.05078	25.196211	29.982244	5.2160986	4.4547798
1.5.7 Phenylalanine metabolism	7.58525	5.182987	5.907649	-0.42507	0.8241103	16.522231	-31.55514	12.200869
1.5.8 Tryptophan metabolism	8.79946	21.22153	60.91776	13.05138	26.308365	29.343788	11.640663	18.550188
1.5.9 Tyrosine metabolism	3.33751	-4.96526	-19.5243	-17.9495	2.7802669	16.506577	-0.901017	28.949064
1.5.10 Valine, leucine and isoleucine biosynthesis	13.6308	5.597965	24.95153	14.45276	36.089164	42.676046	-35.72372	-14.08262
1.5.11 Valine, leucine and isoleucine degradation	3.544461	27.89215	61.64364	58.72809	60.514492	58.735901	54.66852	49.022622
1.6 Metabolism of Other Amino Acids								

1.6.1 beta-Alanine metabolism	22.63711	60.06199	56.50334	54.34965	51.56059	64.292271	5.8984944	15.605972
1.6.2 Glutathione metabolism	-2.25425	51.08528	74.22806	38.76331	132.44632	49.902785	25.871508	21.347741
1.6.3 Selenoamino acid metabolism	12.00314	7.953747	20.297	26.78108	79.334665	57.578016	-9.729332	12.75563
1.6.4 Taurine and hypotaurine metabolism	101.4887	8.864018	101.4887	39.38496	322.00572	177.36809	23.831544	37.478088
1.7 Glycan Biosynthesis and Metabolism								
1.7.1 Glycosaminoglycan biosynthesis - chondroitin sulfate	9.412214	56.25275	1.257932	12.34516	63.227713	34.360453	-13.6707	-8.059027
1.7.2 Glycosaminoglycan biosynthesis - heparan sulfate	-6.53681	10.4794	-84.0194	26.09858	14.07197	72.311772	-26.92059	-17.75338
1.7.3 Glycosaminoglycan biosynthesis - keratan sulfate	22.85244	-7.59453	27.04184	-41.9465	41.026038	58.719795	-12.65547	12.49194
1.7.4 Glycosaminoglycan degradation	21.06001	-14.9608	0.600987	12.93075	-33.51602	11.009833	10.315333	23.042472
1.7.5 Glycosphingolipid biosynthesis - ganglio series	37.06249	50.59335	32.89442	31.8119	90.194901	102.93636	51.22733	13.09792
1.7.6 Glycosphingolipid biosynthesis - globo series	14.29041	0.499682	2.433028	-10.3018	0.2713268	7.9445962	2.433028	1.8939719
1.7.7 Glycosphingolipid biosynthesis - lacto and neolacto series	3.907567	-27.0697	47.86917	-7.75299	53.871846	-3.482261	29.781686	17.497497
1.7.8 Glycosylphosphatidylinositol(GPI)-anchor biosynthesis	-6.49183	217.5557	251.9759	276.2121	389.31054	308.27999	139.08348	106.38206
1.7.9 N-Glycan biosynthesis	-4.43212	17.31203	33.40708	5.706333	81.944623	45.192451	-22.77554	-5.917813
1.7.10 O-Glycan biosynthesis	10.26165	-11.294	-17.2034	-18.2882	-28.44048	17.113878	-7.9751	-7.9751
1.7.11 O-Mannosyl glycan biosynthesis	20.50113	-26.5688	4.424765	-32.968	14.128783	-21.69096	-16.05153	7.1390352
1.7.12 Other glycan degradation	-14.7832	-17.3645	12.67144	39.76685	-6.5565	19.694401	6.646632	13.09792
1.8 Metabolism of Cofactors and Vitamins								
1.8.1 Folate biosynthesis	37.67683	5.744178	-10.4701	22.57979	-47.99643	24.588859	-6.55661	-78.01939
1.8.2 Nicotinate and nicotinamide metabolism	23.75075	16.19965	20.58282	-2.82033	28.892377	49.93916	35.312063	47.999636
1.8.3 One carbon pool by folate	-13.6695	8.124114	-35.723	16.5895	8.0375505	27.475874	-13.6695	-106.5212
1.8.4 Pantothenate and CoA biosynthesis	21.1915	60.8105	1.921309	37.96919	7.8099376	16.897244	-36.03244	-26.69807
1.8.5 Porphyrin and chlorophyll metabolism	13.5862	-48.8551	-39.4681	-65.5885	-121.6769	-107.0676	-45.13689	-59.1724
1.8.6 Retinol metabolism	-2.66947	11.26226	-26.0156	12.05027	82.817605	21.0415	27.117504	-3.496212
1.8.7 Riboflavin metabolism	73.19438	79.35942	157.6801	90.52165	89.968416	123.65612	-37.55582	8.7308074
1.8.8 Vitamin B6 metabolism	198.9522	198.9522	93.85127	146.1947	192.39433	246.53845	284.08689	230.64764

1.11 Xenobiotics Biodegradation and Metabolism								
1.11.1 Drug metabolism - cytochrome P450	-0.15856	-2.28674	-28.6564	-39.7377	-13.22226	-17.1721	82.477531	74.892102
1.11.2 Drug metabolism - other enzymes	9.014181	33.39547	27.35346	71.23671	73.826379	49.107461	-3.824119	-28.84653
1.11.3 Metabolism of xenobiotics by cytochrome P450	-0.17838	2.7742	-55.2871	-68.8478	-41.00426	-56.58345	50.832962	21.328112
2.1 Transcription								
2.1.1 Basal transcription factors	19.23292	9.893578	-5.39118	-27.0356	-18.00133	-15.6304	10.871332	16.1225
2.1.2 RNA polymerase	18.63251	50.61653	35.05102	51.57304	85.264306	68.212475	22.269877	7.0090438
2.1.3 Spliceosome	6.198625	-8.9284	10.54924	-12.7916	-19.40721	-37.40797	-0.158138	9.8227364
2.2 Translation								
2.2.1 Aminoacyl-tRNA biosynthesis	19.9959	23.07224	53.78302	8.533274	15.759428	-25.08692	-29.141	-20.11422
2.2.2 mRNA surveillance pathway	-0.20175	-13.6565	11.64567	-14.1799	0.6258931	-61.64001	-9.07732	-13.01597
2.2.3 Ribosome	146.4002	1.108459	-11.7415	-48.6802	-83.44059	-82.60025	-24.17457	-19.08296
2.2.4 Ribosome biogenesis in eukaryotes	14.81853	-5.94246	-5.81129	-22.3943	-29.95706	-25.18062	-2.608024	7.236012
2.2.5 RNA transport	12.2314	-28.8281	-18.308	-44.9616	-52.48328	-64.03553	-20.1074	1.2722085
2.3 Folding, Sorting and Degradation								
2.3.1 Proteasome	23.0468	10.58038	15.11557	-11.1042	-4.85113	-20.94786	0.3189195	13.275896
2.3.2 Protein export	81.67203	124.4562	96.21458	81.685	125.68163	51.459894	81.67203	10.534866
2.3.3 Protein processing in endoplasmic reticulum	10.04433	36.07438	45.30309	25.49289	44.923683	35.499251	21.60928	-3.007568
2.3.4 RNA degradation	11.42531	-46.8051	-21.1712	-46.4762	-52.41938	-95.87296	-26.14287	-5.703536
2.3.5 SNARE interactions in vesicular transport	8.75943	16.31756	16.44054	-11.1621	-2.612005	-4.30656	24.752084	39.264991
2.3.6 Sulfur relay system	17.04787	-25.8329	-49.1947	-116.693	-168.6621	-132.1567	-26.37581	-71.6954
2.3.7 Ubiquitin mediated proteolysis	0.014252	-3.38828	13.4494	-10.3805	6.8634998	-29.49549	-7.708191	-2.593932
2.4 Replication and Repair								
2.4.1 Base excision repair	31.3711	-45.388	-30.8209	-44.4961	-49.38987	-10.57923	-32.9073	-27.08118
2.4.2 DNA replication	7.718519	-58.649	-72.3942	-53.2174	-34.72451	3.0357134	-53.5854	-28.89626
2.4.3 Homologous recombination	-12.3762	-56.7396	-12.3121	-61.2662	-24.90217	-18.60286	-58.38376	-41.64503

2.4.4 Mismatch repair	29.23926	-23.8245	-39.0646	-39.748	-45.14475	7.0024015	-53.18135	-27.39781
2.4.5 Non-homologous end-joining	3.214387	-73.3593	-28.4587	-30.0641	109.18237	3.214387	3.214387	38.771704
2.4.6 Nucleotide excision repair	21.96915	-13.1883	-21.2271	-32.6573	-16.48169	6.8177307	-16.82508	-13.93032
3.2 Signal Transduction								
3.2.1 Calcium signaling pathway	5.70968	12.69685	24.02861	15.86183	39.356232	21.395252	-8.34703	-0.891712
3.2.2 ErbB signaling pathway	8.409047	18.72056	-2.08513	-13.3901	-1.205284	3.2987321	2.7224075	10.086015
3.2.3 Hedgehog signaling pathway	30.97886	96.53899	130.9727	131.6129	197.6314	138.03358	64.844995	73.302002
3.2.4 Jak-STAT signaling pathway	11.69569	56.89735	63.83007	61.53224	110.96617	52.65462	9.9506239	1.8323729
3.2.5 MAPK signaling pathway	4.732529	2.368287	8.264571	-3.43314	-4.17815	-17.38947	0.5477651	-1.261498
3.2.6 mTOR signaling pathway	18.53542	-31.6068	-35.1797	-48.2185	-68.78811	-40.17782	8.7205242	4.6042565
3.2.7 Notch signaling pathway	-5.1553	-28.796	-45.2202	-55.3534	-73.61042	-46.55709	-11.43642	-0.493014
3.2.8 Phosphatidylinositol signaling system	2.163651	22.38651	23.30569	19.35823	38.867005	27.4763	-2.550985	-8.329861
3.2.9 TGF-beta signaling pathway	3.199988	22.73006	59.31818	9.893538	51.552134	21.047659	48.885841	1.6759717
3.2.10 VEGF signaling pathway	27.50832	36.26665	34.68731	29.16793	45.252239	37.48722	18.42151	14.224665
3.2.11 Wnt signaling pathway	13.65899	-2.83186	7.727558	-13.1819	-7.900756	-17.10398	-13.65034	-11.42578
3.3 Signaling Molecules and Interaction								
3.3.1 Cell adhesion molecules (CAMs)	17.37491	-14.9728	-3.8261	-38.7004	-74.15762	-77.96638	-8.912535	-23.83206
3.3.2 Cytokine-cytokine receptor interaction	15.58893	47.81293	58.98241	53.60071	92.081743	60.968483	21.369365	16.487909
3.3.3 ECM-receptor interaction	11.431	13.52634	-7.35502	9.995798	33.835559	62.079893	85.08181	52.868694
3.3.4 Neuroactive ligand-receptor interaction								
4.1 Transport and Catabolism								
4.1.1 Endocytosis	-6.00272	-20.8252	-12.5481	-33.1967	-45.71367	-35.26049	-4.557502	-14.99077
4.1.2 Lysosome	4.396072	-12.8302	16.00141	-11.1736	-28.08414	-24.14962	13.622027	0.1796
4.1.3 Peroxisome	-0.86315	30.22243	46.66823	51.03351	91.307135	35.249487	-2.518049	17.661952
4.1.4 Phagosome	15.07446	34.08632	36.91097	7.710612	-16.59382	-12.0522	55.44292	0.0466557
4.1.5 Regulation of autophagy	27.71494	60.08543	47.47838	41.71414	65.981283	-3.613997	-12.19072	-5.44992

4.3 Cell Growth and Death								
4.3.1 Apoptosis	6.276713	-4.99884	9.112277	4.883141	19.279232	2.9744484	11.587914	17.580398
4.3.2 Cell cycle	1.772051	-39.6942	-33.4796	-35.8906	-34.95543	-39.00364	-25.55056	-25.71179
4.3.3 Oocyte meiosis	6.845596	-19.1392	-9.68934	-21.4376	-7.955001	-14.05049	-10.33415	-16.38638
4.3.4 p53 signaling pathway	0.536151	19.42779	10.04177	-2.53189	15.299354	-15.55494	24.739222	22.114557
4.4 Cell Communication								
4.4.1 Adherens junction	4.87893	-13.1082	21.67875	3.328848	17.83375	-0.13565	33.952538	-5.066057
4.4.2 Focal adhesion	0.837215	0.452566	-3.26497	-7.69674	-9.851964	-10.12715	35.773491	8.0647456
4.4.3 Gap junction	4.724751	1.916242	5.388109	1.620746	-18.52754	-15.0613	2.9403936	-5.304892
4.4.4 Tight junction	2.356719	23.55393	38.19376	12.46808	43.646038	9.8541085	19.123482	10.449451
5.1 Immune System								
5.1.1 Antigen processing and presentation	15.28675	-67.3984	-77.9916	-141.191	-269.768	-265.9329	-50.59471	-86.43049
5.1.2 B cell receptor signaling pathway	26.45661	30.24563	49.0548	34.14956	82.841275	64.571083	32.049438	17.557608
5.1.3 Chemokine signaling pathway	7.152098	28.05337	30.4045	40.19886	40.720414	35.75997	17.937938	25.4618
5.1.4 Complement and coagulation cascades	7.138365	27.17492	64.22002	58.97386	54.941966	35.797793	11.014494	10.03926
5.1.5 Cytosolic DNA-sensing pathway	36.71381	34.33546	47.13115	44.9932	81.576864	57.301062	3.4967449	-12.17622
5.1.6 Fc epsilon RI signaling pathway	19.3481	56.12042	46.39631	67.73976	123.57867	94.414636	35.265499	22.169116
5.1.7 Fc gamma R-mediated phagocytosis	-1.37369	-15.753	5.922963	-16.7073	-18.72153	-21.56405	16.605207	1.1742871
5.1.8 Hematopoietic cell lineage	24.62263	82.46505	102.9455	76.92447	146.01899	83.886333	20.585072	38.167367
5.1.9 Intestinal immune network for IgA production	24.70608	-35.957	-35.6361	-48.1439	-78.76777	-75.34287	-21.45618	-39.61471
5.1.10 Leukocyte transendothelial migration	8.858655	11.89072	22.14311	15.85255	14.668343	4.36532	22.669049	-7.505356
5.1.11 Natural killer cell mediated cytotoxicity	18.7863	23.79944	37.30805	34.87222	47.278791	34.827355	17.996664	6.946594
5.1.12 NOD-like receptor signaling pathway	20.87939	29.15926	30.73617	30.49239	58.217333	28.437383	11.50472	7.7752351
5.1.13 RIG-I-like receptor signaling pathway	26.25564	47.34097	45.24402	51.03545	117.81147	46.786086	-7.558671	0.3149924
5.1.14 T cell receptor signaling pathway	31.64782	41.05819	35.72503	38.66472	78.09737	59.099559	10.957913	15.596527
5.1.15 Toll-like receptor signaling pathway	24.57004	60.9672	46.78995	55.145	97.157859	80.099479	20.429738	30.145156

5.2 Endocrine System								
5.2.1 Adipocytokine signaling pathway	-16.2173	8.502171	-2.94747	4.06737	29.762183	-43.26602	-36.59154	-10.13653
5.2.2 GnRH signaling pathway	13.0521	40.96834	39.44824	33.72384	72.244248	53.448196	1.5705223	-0.29894
5.2.3 Insulin signaling pathway	11.73105	-7.82295	-9.09077	-17.5749	-23.93207	-17.23087	-4.152365	9.8270623
5.2.4 Melanogenesis	17.75829	18.31077	11.91848	14.62388	38.545818	23.73002	1.4333754	-8.245266
5.2.5 PPAR signaling pathway	-3.34173	111.5771	172.8268	147.0242	149.65294	110.80593	-1.87114	46.328622
5.2.6 Renin-angiotensin system	56.00112	56.00112	46.05366	-8.4254	126.30544	60.070785	56.00112	56.00112
5.3 Circulatory System								
5.3.1 Cardiac muscle contraction	3.907061	1.877218	28.30365	-6.36786	22.12249	10.442091	4.333545	24.066595
5.3.1 Vascular smooth muscle contraction	8.468649	-2.33548	5.99889	-4.52426	12.611082	10.77043	-2.714129	-17.51529
5.4 Digestive System								
5.4.1 Bile secretion	5.969565	24.02151	71.56272	45.93047	85.898791	43.074083	9.1502126	-6.624042
5.4.2 Carbohydrate digestion and absorption	-6.13994	-58.789	32.97095	-49.5203	-24.51101	-54.09499	-6.288118	-23.7675
5.4.3 Fat digestion and absorption	21.28326	125.4648	117.4985	100.3651	199.03267	182.6429	38.023304	43.120524
5.4.4 Gastric acid secretion	-0.31676	-23.7163	13.61379	-14.997	-1.1205	-26.10569	-19.70184	-22.23081
5.4.5 Mineral absorption	20.926	-9.80209	39.26086	-47.3502	-51.32886	-53.58084	-37.02754	10.021937
5.4.6 Pancreatic secretion	9.512353	-4.31076	25.39935	-2.28636	-4.774276	-32.67164	-6.480275	-6.450714
5.4.7 Protein digestion and absorption	-6.40864	7.42127	40.87888	30.98146	0.3749344	32.70419	26.382153	48.546984
5.4.8 Salivary secretion	1.49943	-32.7146	35.01433	-21.187	-16.19568	-49.70269	-12.62109	-22.10101
5.4.9 Vitamin digestion and absorption	-18.8295	-27.8109	-50.3143	-29.0013	-16.42966	-37.83826	-30.0373	-30.0373
5.5 Excretory System								
5.5.1 Aldosterone-regulated sodium reabsorption	-6.55379	-40.142	11.21907	-62.2207	-41.92031	-91.75828	-3.473925	-6.341909
5.5.2 Collecting duct acid secretion	11.27116	92.30035	91.8192	125.6651	154.20239	130.65358	102.79648	54.063536
5.5.3 Endocrine and other factor-regulated calcium reabsorption	-0.10433	-54.3648	26.77251	-59.7955	-44.72387	-72.8691	0.1771249	-17.73222
5.5.4 Proximal tubule bicarbonate reclamation	-32.7189	-194.429	3.136557	-144.806	-129.3552	-266.9931	-168.1325	-67.82574

5.5.5 Vasopressin-regulated water reabsorption	4.835339	-15.438	-14.5051	-28.087	-25.82212	-23.58743	-20.11172	-11.06158
5.6 Nervous System								
5.6.1 Glutamatergic synapse	13.58686	24.23118	32.41749	27.31972	29.521854	9.7289443	-3.556853	9.1474071
5.6.2 Long-term depression	9.50086	15.76663	1.03143	4.456968	-0.366467	20.011909	12.699486	8.4469875
5.6.3 Long-term potentiation	1.152554	-3.74562	16.90656	2.872507	16.286158	3.3326181	1.0013524	-8.280526
5.6.4 Neurotrophin signaling pathway	5.300758	2.079494	15.25824	-1.1812	15.87	12.245888	7.4742536	7.098062
5.8 Development								
5.8.1 Axon guidance	10.421	4.61138	8.911142	3.134757	-3.94731	0.3807133	30.201637	16.958699
5.8.2 Dorso-ventral axis formation	13.51297	7.161628	20.35695	5.15866	5.2280828	-8.113608	51.286092	13.51297
5.8.3 Osteoclast differentiation	9.293031	21.3767	32.84947	36.31285	61.050374	40.862837	12.402501	11.107312

Table S3 (a) The subdivision of total effect between KEGG pathway categories and subcategories. The direct effect has been marked using the red frame.

1. Metabolism

	Subdivision of the total effect										
	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	1.11
The direct effect and indirect effect	-0.2173	-0.1552	-0.20652	-0.20785	-0.21623	-0.19432	-0.20358	-0.18228	-0.0228	-0.04222	-0.21316
	-0.08497	-0.11897	-0.08486	-0.10254	-0.08291	-0.06743	-0.07706	-0.08916	-0.00834	-0.02738	-0.09415
	-1.73787	-1.30434	-1.82859	-1.73958	-1.739	-1.74349	-1.81594	-1.56739	-0.16081	-0.27927	-1.76854
	1.133145	1.020998	1.126982	1.184643	1.118005	0.999081	1.092547	1.033367	0.016755	0.208918	1.158544
	0.7876	0.551609	0.752721	0.746974	0.791497	0.723868	0.739905	0.634213	0.140227	0.150867	0.775614
	-0.19773	-0.12532	-0.21082	-0.18647	-0.20222	-0.22111	-0.21294	-0.16996	-0.04704	-0.01271	-0.19943
	1.823331	1.260598	1.932784	1.794936	1.819378	1.87436	1.94624	1.675157	0.066076	0.191349	1.836057
	0.06773	0.060507	0.069209	0.070432	0.064697	0.062064	0.069496	0.080742	-0.00517	0.00344	0.070364
	0.025238	0.016853	0.021153	0.003402	0.042614	0.05117	0.008166	-0.01539	0.240533	0.079588	0.039217
	0.008312	0.009847	0.006534	0.007545	0.008155	0.002459	0.004206	0.001823	0.014156	0.042782	0.006585
	-0.61313	-0.49461	-0.60452	-0.61127	-0.6125	-0.56375	-0.58966	-0.5447	-0.10191	-0.09621	-0.62504
Total effect	0.99436	0.721972	0.974076	0.960212	0.991487	0.922905	0.961381	0.856431	0.13169	0.219149	0.986067

2. Genetic information processing

	Subdivision of the total effect			
	2.1	2.2	2.3	2.4
The direct effect and indirect effect	0.1086035	0.106688	0.106558	0.099761
	0.2781571	0.283152	0.26908	0.242072
	0.3594356	0.348128	0.366334	0.340384
	2.47E-01	2.29E-01	2.49E-01	2.68E-01
Total effect	0.9927005	0.967389	0.991317	0.950571

3. Environmental information processing

	Subdivision of the total effect		
	3.1	3.2	3.3
The direct effect and indirect effect	0.1400214	0.139352	0.133447
	0.6722134	0.675443	0.655844
	0.181026	0.184433	0.189944
Total effect	0.9932608	0.999228	0.979235

4. Cellular processes

	Subdivision of the total effect			
	4.1	4.2	4.3	4.4
The direct effect and indirect effect	0.3686887	0.333784	0.357229	0.360226
	0.0633081	0.069928	0.066672	0.067989
	0.2676331	0.263355	0.276219	0.271672
	2.89E-01	2.88E-01	2.91E-01	2.96E-01
Total effect	0.9888705	0.954893	0.991281	0.995923

5. Organismal systems

	Subdivision of the total effect								
	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9
The direct effect and indirect effect	3.7013617	3.61967	3.407391	3.533839	3.355024	3.611378	3.370509	3.662398	2.058651
	74.641538	76.32612	71.887	74.45375	71.10105	74.98975	73.46354	75.13974	42.23142
	-13.52652	-13.8389	-14.6935	-13.4651	-14.5189	-13.3903	-12.732	-13.7924	-8.31358
	-26.62131	-27.1993	-25.5523	-27.8833	-26.1276	-27.3711	-25.326	-26.378	-13.3612
	8.9705003	9.219034	9.778944	9.273392	9.896522	8.979793	8.387507	9.024414	5.504415
	-0.449581	-0.45272	-0.41991	-0.45232	-0.4181	-0.46078	-0.41882	-0.45126	-0.21713
	-19.10572	-20.1943	-18.1803	-19.0568	-17.782	-19.0703	-20.9812	-19.3299	-12.551
	-26.29892	-26.1656	-24.9487	-25.1438	-24.2365	-26.0292	-24.4869	-26.5787	-14.2191
	-0.322075	-0.3204	-0.32764	-0.27748	-0.32208	-0.27288	-0.34641	-0.30979	-0.57908
Total effect	0.9892694	0.993619	0.951076	0.982096	0.947343	0.986382	0.93035	0.986601	0.553443

Table S3 (b) The subdivision of total effect between KEGG pathway subcategories and its secondary pathways. The direct effect has been marked using the red frame.

1.1 Carbohydrate Metabolism

	Subdivision of the total effect													
	1.1.1	1.1.2	1.1.3	1.1.4	1.1.5	1.1.6	1.1.7	1.1.8	1.1.9	1.1.10	1.1.11	1.1.12	1.1.13	1.1.14
The direct effect and indirect effect	-0.983081	-0.83708	-0.33582	-0.87695	-0.70491	-0.754242	-0.90322	-0.85596	-0.89046	-0.89659	-0.55326	-0.96737	-0.86842	-0.78085
	0.1870352	0.219657	0.086639	0.196974	0.200865	0.1877005	0.197131	0.176059	0.200212	0.21221	0.170855	0.189821	0.210647	0.137888
	-0.032043	-0.037	-0.0938	-0.03825	-0.05174	-0.031228	-0.03311	-0.05052	-0.05086	-0.02698	-0.06829	-0.02496	-0.03393	-0.03025
	-0.025512	-0.02565	-0.01166	-0.0286	-0.02027	-0.027634	-0.02771	-0.02671	-0.02636	-0.02672	-0.01783	-0.02635	-0.02749	-0.01441
	-0.575235	-0.73361	-0.44254	-0.56863	-0.80224	-0.515406	-0.5512	-0.52657	-0.6811	-0.66919	-0.6427	-0.54695	-0.65688	-0.53023
	-0.172242	-0.19184	-0.07474	-0.21693	-0.14423	-0.2245	-0.20312	-0.19858	-0.19187	-0.19497	-0.12686	-0.18311	-0.205	-0.08041
	-0.520365	-0.50829	-0.19993	-0.54884	-0.38914	-0.512432	-0.56637	-0.51804	-0.50862	-0.53059	-0.37236	-0.54414	-0.53142	-0.31622
	0.0970248	0.089316	0.060022	0.104055	0.073143	0.0985665	0.101924	0.111434	0.105682	0.091122	0.066242	0.098262	0.092481	0.066287
	0.7983706	0.80339	0.477947	0.812533	0.748318	0.7532967	0.791542	0.835921	0.881415	0.799073	0.59095	0.790801	0.790714	0.618923
	-0.246437	-0.26105	-0.07771	-0.25242	-0.2254	-0.234666	-0.25314	-0.22096	-0.24497	-0.27021	-0.17385	-0.25289	-0.26619	-0.16263
	0.1635233	0.226008	0.211528	0.181202	0.232781	0.1641904	0.191032	0.172725	0.19481	0.186947	0.290563	0.157729	0.198353	0.13882
	0.6530029	0.573473	0.176596	0.611511	0.452434	0.5412524	0.637563	0.585169	0.595386	0.621073	0.360233	0.663609	0.601043	0.467993
	1.3512527	1.466913	0.55338	1.47012	1.252499	1.3967609	1.435264	1.269494	1.372248	1.50691	1.044222	1.385439	1.529655	0.805393
	0.2190373	0.17311	0.088927	0.138905	0.182264	0.0987689	0.153969	0.164042	0.193641	0.16598	0.131751	0.194477	0.145196	0.275767
Total effect	0.9143338	0.957353	0.418832	0.984679	0.804375	0.9404283	0.970552	0.917509	0.949156	0.968067	0.699658	0.934366	0.978754	0.596077

1.2 Energy Metabolism

	Subdivision of the total effect		
	1.2.1	1.2.2	1.2.3
The direct effect and indirect effect	0.2055539	0.049664	0.137621
	0.1346169	0.557162	0.189626
	0.282102	0.143405	0.421355
Total effect	0.6222728	0.750231	0.748601

1.3 Lipid Metabolism

	Subdivision of the total effect												
	1.3.1	1.3.2	1.3.3	1.3.4	1.3.5	1.3.6	1.3.7	1.3.8	1.3.9	1.3.10	1.3.11	1.3.12	1.3.13
The direct effect and indirect effect	0.8228026	0.651099	0.437361	0.700585	0.59483	0.5946502	0.556987	0.675845	-0.14232	0.601156	0.634911	0.789235	0.336941
	4.2334603	5.349885	4.176953	4.933566	3.734289	4.9938103	5.105388	5.124942	0.901247	5.140165	4.37517	3.567458	3.040561
	0.393377	0.577802	0.740055	0.559911	0.584409	0.546862	0.569949	0.544039	0.168595	0.623242	0.659752	0.351029	0.623648
	0.5928272	0.642066	0.526766	0.696247	0.486878	0.5658106	0.620514	0.68284	-0.03383	0.628433	0.588101	0.526726	0.459349
	-0.350337	-0.33826	-0.38269	-0.33888	-0.48461	-0.259353	-0.25979	-0.3175	0.088186	-0.39433	-0.4248	-0.3229	-0.34134
	-0.916679	-1.18396	-0.93727	-1.03076	-0.67882	-1.268385	-1.20003	-1.09532	-0.47583	-1.03812	-0.90522	-0.80338	-0.58724
	-2.122876	-2.99267	-2.41517	-2.79488	-1.68115	-2.966989	-3.13599	-2.96939	-1.0987	-2.76749	-2.22309	-1.66928	-1.60328
	0.1494052	0.174244	0.133715	0.17839	0.119169	0.1570732	0.172229	0.181892	0.016422	0.167579	0.143212	0.124559	0.101354
	-0.160876	0.156678	0.211879	-0.04519	-0.16925	0.3489096	0.325848	0.083968	0.930056	0.067236	-0.02983	-0.26347	-0.23148
	-1.279192	-1.6822	-1.47447	-1.5803	-1.42469	-1.432985	-1.5451	-1.61306	-0.12657	-1.75083	-1.52739	-1.04717	-1.17985
	-0.718796	-0.7618	-0.83043	-0.78682	-0.81655	-0.664804	-0.66035	-0.73342	0.029877	-0.81263	-0.93151	-0.70396	-0.73826
	-0.200767	-0.13957	-0.09928	-0.15834	-0.13946	-0.132571	-0.11141	-0.14333	0.059292	-0.12519	-0.15818	-0.20931	-0.09306
	0.372828	0.51744	0.767231	0.600663	0.641288	0.4215195	0.465462	0.507314	-0.22659	0.613526	0.721556	0.404791	0.910439
Total effect	0.8151787	0.970749	0.854653	0.934181	0.766349	0.9035484	0.90371	0.928826	0.089821	0.952738	0.922676	0.744331	0.697787

1.4 Nucleotide Metabolism

	Subdivision of the total effect	
	1.4.1	1.4.2
The direct effect and indirect effect	0.6097897	0.565585
	3.79E-01	4.08E-01
Total effect	0.9882966	0.973675

1.5 Amino Acid Metabolism

	Subdivision of the total effect										
	1.5.1	1.5.2	1.5.3	1.5.4	1.5.5	1.5.6	1.5.7	1.5.8	1.5.9	1.5.10	1.5.11
The direct effect and indirect effect	-0.488657	-0.27364	-0.24165	-0.3291	-0.19492	-0.307177	0.15488	-0.2086	-0.05028	-0.36078	-0.33423
	0.6717418	1.199581	0.873406	0.777203	1.04841	1.1021067	0.071663	1.011801	0.438843	0.926075	0.89562
	-0.23891	-0.35175	-0.48311	-0.40266	-0.37328	-0.351225	-0.03484	-0.33072	-0.14703	-0.32789	-0.32374
	0.6246859	0.600949	0.773082	0.92754	0.737949	0.7560728	0.163336	0.657368	0.354361	0.840248	0.756761
	0.4496745	0.985278	0.871051	0.896915	1.127346	0.9966308	0.511656	1.043912	0.701563	0.909973	0.924148
	-1.351036	-1.97459	-1.56249	-1.75192	-1.90003	-2.149229	-0.0683	-1.8872	-0.83745	-2.03571	-1.74731
	0.2485013	-0.04684	-0.05653	-0.13807	-0.35584	-0.024917	-0.78404	-0.26033	-0.52156	-0.02766	-0.21744
	-0.143877	-0.28428	-0.23072	-0.23886	-0.31209	-0.295944	-0.11191	-0.33704	-0.25729	-0.27261	-0.29624
	0.0463094	0.16466	0.136984	0.171958	0.280103	0.1753828	0.299417	0.343596	0.450099	0.179968	0.319546
	0.7265173	0.759664	0.667854	0.891415	0.794284	0.9320475	0.034717	0.795932	0.393451	0.984022	0.838891
	0.0799684	0.087292	0.078349	0.095391	0.095844	0.0950536	0.032426	0.102765	0.083005	0.099674	0.116918
Total effect	0.6249187	0.866328	0.826214	0.899804	0.947778	0.9288016	0.26901	0.931494	0.607713	0.915304	0.932927

1.6 Metabolism of Other Amino Acids

	Subdivision of the total effect			
	1.6.1	1.6.2	1.6.3	1.6.4
The direct effect and indirect effect	0.0955052	0.081205	0.067552	0.05978
	0.5366623	0.631172	0.545657	0.51347
	-0.028986	-0.03543	-0.04098	-0.02891
	2.30E-01	2.99E-01	2.59E-01	3.68E-01
Total effect	0.8334136	0.97618	0.831674	0.912168

1.7 Glycan Biosynthesis and Metabolism

	Subdivision of the total effect											
	1.7.1	1.7.2	1.7.3	1.7.4	1.7.5	1.7.6	1.7.7	1.7.8	1.7.9	1.7.10	1.7.11	1.7.12
The direct effect and indirect effect	0.0122022	0.009396	0.009293	0.009919	0.00857	0.0077258	0.011077	0.011226	0.010055	0.006435	0.009958	0.007809
	0.1001585	0.130068	0.089115	0.110621	0.096461	0.1049041	0.11642	0.109875	0.124731	0.058189	0.104947	0.091882
	-0.015589	-0.01402	-0.02047	-0.0185	-0.01666	-0.015534	-0.01646	-0.01523	-0.0168	-0.01715	-0.01707	-0.01501
	0.0365071	0.038195	0.040591	0.044909	0.039225	0.0394652	0.041495	0.035196	0.042989	0.032762	0.03745	0.038978
	-0.299362	-0.3161	-0.347	-0.37228	-0.42623	-0.402545	-0.38644	-0.33836	-0.36954	-0.36743	-0.3785	-0.35612
	0.1477641	0.188229	0.177109	0.205089	0.220412	0.2333807	0.2022	0.1806	0.208466	0.190947	0.195794	0.176594
	0.1194538	0.117776	0.105829	0.121579	0.119298	0.1140021	0.131582	0.121501	0.125898	0.087103	0.120429	0.107936
	0.2972892	0.272963	0.240346	0.253242	0.256509	0.2500504	0.298371	0.323128	0.276636	0.201419	0.298284	0.18173
	-0.118352	-0.13773	-0.1179	-0.13748	-0.12452	-0.128291	-0.13742	-0.12296	-0.14362	-0.09155	-0.1226	-0.12091
	0.0876874	0.074385	0.139305	0.121296	0.143334	0.1360394	0.110065	0.103644	0.105987	0.166271	0.122117	0.10244
	0.2944352	0.291115	0.300913	0.300869	0.320397	0.3026898	0.330215	0.333058	0.307985	0.264988	0.360798	0.227485

	0.2208175	0.243755	0.253016	0.299482	0.288301	0.2610989	0.28305	0.194064	0.290482	0.212593	0.217561	0.345059
Total effect	0.8830118	0.898023	0.870151	0.938744	0.92509	0.9029858	0.984156	0.935752	0.963261	0.744572	0.949163	0.787875

1.8 Metabolism of Cofactors and Vitamins

	Subdivision of the total effect							
	1.8.1	1.8.2	1.8.3	1.8.4	1.8.5	1.8.6	1.8.7	1.8.8
The direct effect and indirect effect	-0.307106	-0.13488	-0.26984	-0.01385	-0.14268	-0.017105	0.176055	-0.08403
	-0.462354	-1.05272	-0.16399	-0.75966	-0.80537	-0.643109	0.185587	-0.27697
	-1.37345	-0.24351	-1.56313	-0.09271	-0.58382	-0.072797	0.915049	-0.38865
	-0.002803	-0.04485	-0.00369	-0.06215	-0.04866	-0.05311	-0.00113	-0.00804
	1.6540298	2.72374	1.329722	2.787455	3.560246	3.1355086	0.352321	-0.22151
	-0.060188	-0.66015	-0.05032	-0.92344	-0.95169	-1.080603	-0.34301	0.257602
	1.0457309	0.321585	1.067847	-0.03302	-0.18052	-0.579026	-1.82415	1.473334
	-0.171014	-0.16444	-0.1554	-0.08084	0.038887	0.1489918	0.504803	-0.625
Total effect	0.3228447	0.744787	0.191196	0.821781	0.886406	0.8387491	-0.03447	0.126729

1.11 Xenobiotics Biodegradation and Metabolism

	Subdivision of the total effect		
	1.11.1	1.11.2	1.11.3
The direct effect and indirect effect	0.251367	0.157791	0.221724
	0.3545104	0.564749	0.46874
	0.2353527	0.221458	0.266818
Total effect	0.8412301	0.943998	0.957282

2.1 Transcription

	Subdivision of the total effect		
	2.1.1	2.1.2	2.1.3
The direct effect and indirect effect	0.2481747	0.20318	0.2179
	0.2747644	0.335611	0.311743
	0.3996707	0.422827	0.455201
Total effect	0.9226099	0.961619	0.984844

2.2 Translation

	Subdivision of the total effect				
	2.2.1	2.2.2	2.2.3	2.2.4	2.2.5
The direct effect and indirect effect	0.2032147	0.169095	-0.00524	0.152403	0.126709
	0.3132889	0.376504	0.08316	0.351887	0.3376
	-0.008265	0.07082	0.320636	0.15544	0.083574
	0.1474029	0.183696	0.095283	0.196547	0.178367
	0.0929949	0.133734	0.038875	0.135349	0.149144
Total effect	0.7486367	0.933848	0.532715	0.991626	0.875395

2.3 Folding, Sorting and Degradation

	Subdivision of the total effect						
	2.3.1	2.3.2	2.3.3	2.3.4	2.3.5	2.3.6	2.3.7
The direct effect and indirect effect	-0.195811	-0.00219	-0.12963	-0.15349	-0.17208	-0.12432	-0.14435
	-6.84E-06	-0.00061	-0.00029	-0.00025	-0.00022	-4.20E-05	-0.00032
	0.0377758	0.026899	0.057063	0.047088	0.049686	0.0478337	0.054567
	0.0673414	0.035186	0.07089	0.085906	0.077725	0.0600375	0.076466
	0.3320694	0.136247	0.329021	0.341879	0.377867	0.2709949	0.339655
	0.0846583	0.009139	0.111776	0.093189	0.095629	0.1333418	0.105393
	0.4101807	0.290606	0.532067	0.495259	0.500136	0.4397804	0.556402
Total effect	0.7362079	0.495277	0.9709	0.909576	0.928744	0.8276265	0.987812

2.4 Replication and Repair

	Subdivision of the total effect					
	2.4.1	2.4.2	2.4.3	2.4.4	2.4.5	2.4.6
The direct effect and indirect effect	0.1316413	0.102897	0.109459	0.107411	0.057878	0.1073617
	2.66E-01	0.339926	0.301652	0.272955	0.186377	3.15E-01
	0.3164548	0.337733	0.380585	0.338535	0.26685	0.3554114
	0.0325373	0.032021	0.035471	0.039877	0.018894	0.034121
	0.0833251	0.103911	0.132883	0.089793	0.18952	0.1063559
	0.0190363	0.021646	0.021797	0.019972	0.013099	0.0233413
Total effect	0.8486971	0.938134	0.981848	0.868544	0.732616	0.9418291

3.2 Signal Transduction

	Subdivision of the total effect										
	3.2.1	3.2.2	3.2.3	3.2.4	3.2.5	3.2.6	3.2.7	3.2.8	3.2.9	3.2.10	3.2.11
The direct effect and indirect effect	-1.554134	-1.53106	-1.48585	-1.52707	-1.53367	-1.471554	-1.50774	-1.52028	-1.36328	-1.49227	-1.52515
	-0.899481	-0.91304	-0.87275	-0.90793	-0.89823	-0.853664	-0.87999	-0.88587	-0.80504	-0.86388	-0.89216
	-0.101792	-0.10177	-0.10647	-0.10151	-0.10366	-0.090636	-0.10161	-0.10256	-0.10002	-0.09516	-0.10265
	0.8615277	0.871891	0.835947	0.876797	0.864713	0.836275	0.853661	0.8581	0.794701	0.8098	0.843748
	0.4722035	0.47074	0.465861	0.471908	0.478503	0.4429598	0.456932	0.475117	0.428782	0.451988	0.469083
	-0.228845	-0.22597	-0.20575	-0.23052	-0.22373	-0.241688	-0.22685	-0.2275	-0.20336	-0.21232	-0.21671
	1.5768083	1.566489	1.551094	1.582437	1.552052	1.5255181	1.625324	1.546965	1.541898	1.419051	1.517215
	0.4816325	0.477703	0.474287	0.481857	0.488872	0.4634535	0.468619	0.492356	0.446512	0.456321	0.478373
	-0.479779	-0.48225	-0.51381	-0.49573	-0.49011	-0.460197	-0.51887	-0.49602	-0.54694	-0.4081	-0.47002
	0.2605137	0.256706	0.242493	0.250583	0.25628	0.2383485	0.236881	0.251457	0.202439	0.271314	0.264844
	0.6028374	0.600246	0.592254	0.591139	0.6022	0.5508173	0.573434	0.596847	0.527895	0.599645	0.614294
Total effect	0.991491	0.989688	0.977298	0.99196	0.993218	0.9396332	0.979795	0.98861	0.923583	0.936391	0.980865

3.3 Signaling Molecules and Interaction

	Subdivision of the total effect			
	3.3.1	3.3.2	3.3.3	3.3.4
The direct effect and indirect effect	0.3958516	0.379141	0.346131	0.388052
	0.2808861	0.293266	0.246311	0.269711
	0.3049745	0.292939	0.348783	0.292561
	8.24E-07	7.73E-07	7.05E-07	8.41E-07

Total effect	0.981713	0.965347	0.941226	0.950325

4.1 Transport and Catabolism

	Subdivision of the total effect				
	4.1.1	4.1.2	4.1.3	4.1.4	4.1.5
The direct effect and indirect effect	-0.008509	-0.00835	-0.0083	-0.00802	-0.00494
	0.134764	0.137324	0.130871	0.128916	0.077317
	0.335617	0.32784	0.344008	0.316224	0.231827
	0.3919071	0.390391	0.382268	0.415855	0.157226
	0.1240657	0.120432	0.144148	0.080872	0.213902
Total effect	0.9778453	0.967638	0.992994	0.933848	0.675337

4.3 Cell Growth and Death

	Subdivision of the total effect			
	4.3.1	4.3.2	4.3.3	4.3.4
The direct effect and indirect effect	0.2199185	0.205898	0.208306	0.202708
	0.2468875	0.263699	0.258279	0.245443
	0.2570327	0.265784	0.271361	0.236976
	2.51E-01	2.53E-01	2.38E-01	2.72E-01
Total effect	0.9745292	0.988528	0.975458	0.957102

4.4 Cell Communication

	Subdivision of the total effect			
	4.4.1	4.4.2	4.4.3	4.4.4
The direct effect and indirect effect	0.1492718	0.14658	0.144729	0.142119
	0.2406451	0.245064	0.232677	0.233225
	0.3014304	0.295178	0.310892	0.304209
	2.94E-01	2.94E-01	3.02E-01	3.09E-01
Total effect	0.9850852	0.98044	0.990188	0.988075

5.1 Immune System

	Subdivision of the total effect														
	5.1.1	5.1.2	5.1.3	5.1.4	5.1.5	5.1.6	5.1.7	5.1.8	5.1.9	5.1.10	5.1.11	5.1.12	5.1.13	5.1.14	5.1.15
The direct effect and indirect effect	1.5336	1.4616	1.4504	1.3983	1.2405	1.4817	1.4964	1.3614	1.4495	1.4698	1.4304	1.4343	1.3258	1.4112	1.4489
	6.5007	6.8209	6.6814	6.2055	6.1231	6.7553	6.7463	6.4402	6.6515	6.7238	6.5088	6.6380	6.4712	6.7040	6.6575
	-13.9493	-14.4473	-14.7490	-13.9776	-12.6633	-14.4765	-14.4708	-14.3404	-14.7119	-14.6582	-14.5526	-14.5542	-13.4061	-14.3720	-14.5962
	0.0773	0.0772	0.0804	0.0848	0.0669	0.0794	0.0776	0.0813	0.0804	0.0788	0.0780	0.0766	0.0703	0.0752	0.0790
	-1.6393	-1.8194	-1.7401	-1.5981	-2.0267	-1.8162	-1.6959	-1.8141	-1.7811	-1.7385	-1.6959	-1.7875	-1.9580	-1.8762	-1.8111
	-10.4790	-10.7414	-10.6453	-10.1552	-9.7192	-10.8457	-10.6897	-10.3899	-10.6581	-10.6090	-10.4342	-10.5819	-10.2916	-10.6441	-10.7151
	-0.1765	-0.1788	-0.1774	-0.1654	-0.1513	-0.1782	-0.1808	-0.1668	-0.1762	-0.1785	-0.1748	-0.1762	-0.1634	-0.1749	-0.1762
	6.7451	7.1738	7.3873	7.2779	6.8010	7.2785	7.0067	7.5978	7.4223	7.2514	7.1715	7.2034	7.0341	7.2127	7.3446
	-14.7563	-15.2242	-15.5726	-14.7946	-13.7199	-15.3418	-15.2116	-15.2513	-15.6119	-15.4329	-15.4531	-15.4683	-14.3086	-15.2871	-15.5375
	9.4644	9.7346	9.8144	9.1695	8.4708	9.6596	9.7506	9.4248	9.7619	9.8752	9.6207	9.6667	8.9702	9.5567	9.6559
	1.0231	1.0467	1.0822	1.0088	0.9178	1.0552	1.0605	1.0353	1.0857	1.0686	1.0969	1.0900	0.9583	1.0644	1.0846
	-5.8849	-6.1236	-6.2092	-5.6809	-5.5497	-6.1393	-6.1300	-5.9656	-6.2344	-6.1594	-6.2531	-6.2923	-5.7717	-6.2313	-6.2611
	-1.8443	-2.0239	-1.9391	-1.7675	-2.0610	-2.0243	-1.9277	-1.9750	-1.9552	-1.9378	-1.8637	-1.9568	-2.1333	-2.0449	-1.9879
	2.2716	2.4262	2.4054	2.1881	2.2852	2.4226	2.3876	2.3434	2.4171	2.3889	2.3954	2.4446	2.3662	2.4685	2.4427
	22.0771	22.8070	23.1245	21.7496	20.8805	23.0852	22.7668	22.5878	23.2552	22.8477	23.1046	23.2508	21.7742	23.1224	23.3665
Total	0.9632	0.9893	0.9933	0.9432	0.8947	0.9957	0.9860	0.9690	0.9950	0.9897	0.9789	0.9872	0.9375	0.9846	0.9946

5.2 Endocrine System

	Subdivision of the total effect					
	5.2.1	5.2.2	5.2.3	5.2.4	5.2.5	5.2.6
The direct effect and indirect effect	0.0584725	0.056659	0.056317	0.052135	0.056614	0.0565897
	5.31E-01	0.547961	0.534053	0.522621	0.489875	5.39E-01
	0.7443037	0.753181	0.772795	0.741498	0.692063	0.7690844
	-0.175692	-0.18794	-0.18907	-0.19705	-0.15684	-0.189099
	0.1927508	0.177976	0.178281	0.158457	0.199079	0.1799426
	-0.358094	-0.36427	-0.36823	-0.35508	-0.33444	-0.370008
Total effect	0.9927068	0.983572	0.984145	0.922583	0.946346	0.985968

5.3 Circulatory System

	Subdivision of the total effect	
	5.3.1	5.3.2
The direct effect and indirect effect	0.4850854	0.382071
	0.450701	0.57222
Total effect	0.9357864	0.95429

5.4 Digestive System

	Subdivision of the total effect								
	5.4.1	5.4.2	5.4.3	5.4.4	5.4.5	5.4.6	5.4.7	5.4.8	5.4.9
The direct effect and indirect effect	1.093932	0.795372	1.060006	1.073221	1.018569	1.0756037	0.817905	1.07678	0.588437
	-0.174846	-0.24048	-0.18897	-0.17945	-0.17484	-0.180233	-0.22391	-0.19295	-0.10927
	-0.07627	-0.06185	-0.07871	-0.07784	-0.06954	-0.076644	-0.06178	-0.07804	-0.04927
	0.3892531	0.296074	0.392362	0.396765	0.349397	0.3913932	0.28838	0.392481	0.22125
	-0.590936	-0.46142	-0.56072	-0.55889	-0.63466	-0.571807	-0.53502	-0.56983	-0.32912
	0.7226202	0.550815	0.715635	0.724983	0.662151	0.7349337	0.537271	0.72416	0.37247
	0.5884812	0.732849	0.617752	0.572073	0.663518	0.5753943	0.787082	0.623452	0.466682
	-0.994932	-0.81099	-1.00216	-0.99987	-0.90753	-0.995963	-0.80064	-1.01078	-0.60609
	0.0266016	0.022472	0.030959	0.027577	0.025645	0.0250635	0.029322	0.029654	0.049454
Total effect	0.9839043	0.822842	0.986154	0.978576	0.932716	0.9777422	0.838607	0.994935	0.604538

5.5 Excretory System

	Subdivision of the total effect				
	5.5.1	5.5.2	5.5.3	5.5.4	5.5.5
The direct effect and indirect effect	0.2225289	0.165823	0.217543	0.190152	0.136588
	0.1046181	0.140394	0.110918	0.11705	0.119928
	0.201356	0.162727	0.205971	0.192287	0.14798
	0.3713081	0.36228	0.405663	0.434531	0.369111
	0.0320721	0.044635	0.03754	0.044385	0.052252

Total effect	0.9318831	0.875859	0.977636	0.978405	0.825858

5.6 Nervous System

	Subdivision of the total effect			
	5.6.1	5.6.2	5.6.3	5.6.4
The direct effect and indirect effect	0.2948841	0.28978	0.293564	0.291829
	0.272576	0.277377	0.275102	0.271881
	0.2374686	0.23658	0.238536	0.236316
	0.191546	0.189717	0.19175	0.193551
Total effect	0.9964747	0.993453	0.998952	0.993577

5.8 Development

	Subdivision of the total effect		
	5.8.1	5.8.2	5.8.3
The direct effect and indirect effect	0.5768827	0.435098	0.540529
	-0.025814	-0.03423	-0.02353
	0.4316671	0.316674	0.460699
Total effect	0.9827359	0.717546	0.977702

Table S4 (a) In the KEGG pathway subcategories, the detailed comparisons between the total effect from KEGG-PATH approach and the average impact values from DIA method, and the impact direction results produced by the DIA method and the gradient analysis. The sign "+" and "-" represent the up-regulating and down-regulating impact direction, respectively.

KEGG pathway category	KEGG pathway sub-category	Impact direction		Impact values	
		DIA direction	gradient direction	DIA average value	total effect
1.Metabolism	1.1 Carbohydrate Metabolism	+	–	110.0823	0.9944
	1.2 Energy Metabolism	–	+	85.8557	0.7200
	1.3 Lipid Metabolism	+	+	97.8102	0.9741
	1.4 Nucleotide Metabolism	–	+	61.5583	0.9602
	1.5 Amino Acid Metabolism	+	–	62.4140	0.9915
	1.6 Metabolism of Other Amino Acids	+	+	83.7617	0.9229
	1.7 Glycan Biosynthesis and Metabolism	+	+	88.5044	0.9614
	1.8 Metabolism of Cofactors and Vitamins	+	+	98.8260	0.8564
	1.9 Metabolism of Terpenoids and Polyketides	+	–	87.3283	0.1317
	1.10 Biosynthesis of Other Secondary Metabolites	+	+	741.8776	0.2191
	1.11 Xenobiotics Biodegradation and Metabolism	+	–	97.3782	0.9861
2. Genetic Information Processing	2.1 Transcription	+	+	38.0857	0.9927
	2.2 Translation	–	+	60.7424	0.9700
	2.3 Folding, Sorting and Degradation	+	+	56.0527	0.9913
	2.4 Replication and Repair	–	–	63.0313	0.9506
3. Environmental Information	3.1 Membrane transport	+	–	153.1934	0.9933

Processing	3.2 Signal Transduction	+	–	83.3863	0.9992
	3.3 Signaling Molecules and Interaction	+	+	104.5405	0.9792
4. Cellular Processes	4.1 Transport and Catabolism	+	+	82.8327	0.9889
	4.2 Cell Motility	–	–	69.9331	0.9500
	4.3 Cell Growth and Death	–	+	74.7252	0.9913
	4.4 Cell Communication	+	+	73.8688	0.9959
5. Organismal Systems	5.1 Immune System	+	+	88.4588	0.9893
	5.2 Endocrine System	+	+	110.3462	0.9900
	5.3 Circulatory System	+	+	63.0967	0.9511
	5.4 Digestive System	+	+	81.7042	0.9821
	5.5 Excretory System	–	+	105.7730	0.9473
	5.6 Nervous System	+	+	76.9902	0.9864
	5.7 Sensory System	–	–	74.7592	0.9304
	5.8 Development	+	+	82.5103	0.9866
	5.9 Environmental Adaptation	–	–	34.2857	0.5534

Table S4 (b) In the secondary KEGG pathways, the detailed comparisons between the total effect from KEGG-PATH approach and the average impact values from DIA method, and the impact direction results produced by the DIA method and the gradient analysis. The sign "+" and "-" represent the up-regulating and down-regulating impact direction, respectively.

1. Metabolism

KEGG pathway subcategory	The secondary pathways	Impact direction		Impact values	
		DIA direction	gradient direction	DIA average value	total effect
1.1 Carbohydrate Metabolism	1.1.1 Amino sugar and nucleotide sugar metabolism	+	+	64.4112	0.9143
	1.1.2 Ascorbate and aldarate metabolism	–	–	171.2486	0.9574
	1.1.3 Butanoate metabolism	+	+	93.7056	0.4188
	1.1.4 Citrate cycle (TCA cycle)	+	+	175.4795	0.9847
	1.1.5 Fructose and mannose metabolism	+	–	83.1190	0.8044
	1.1.6 Galactose metabolism	+	–	346.6752	0.9404
	1.1.7 Glycolysis / Gluconeogenesis	–	+	85.4616	0.9706
	1.1.8 Glyoxylate and dicarboxylate metabolism	–	+	64.5950	0.9175
	1.1.9 Inositol phosphate metabolism	+	+	80.2668	0.9492
	1.1.10 Pentose and glucuronate interconversions	+	+	109.9916	0.9681
	1.1.11Pentose phosphate pathway	–	+	27.6013	0.6997
	1.1.12 Propanoate metabolism	+	+	59.3286	0.9344
	1.1.13 Pyruvate metabolism	–	+	95.5018	0.9788
	1.1.14 Starch and sucrose metabolism	–	+	95.5789	0.5961
1.2 Energy Metabolism	1.2.1 Nitrogen metabolism	–	–	43.8307	0.6223

	1.2.2 Oxidative phosphorylation	+	–	73.8002	0.7502
	1.2.3 Sulfur metabolism	–	+	155.1852	0.7486
1.3 Lipid Metabolism	1.3.1 alpha-Linolenic acid metabolism	+	–	53.8355	0.8152
	1.3.2 Arachidonic acid metabolism	+	–	102.7344	0.9707
	1.3.3 Biosynthesis of unsaturated fatty acids	+	–	223.7080	0.8547
	1.3.4 Ether lipid metabolism	+	–	103.3507	0.9342
	1.3.5 Fatty acid elongation in mitochondria	–	+	69.6165	0.7663
	1.3.6 Fatty acid metabolism	–	–	62.6484	0.9035
	1.3.7 Glycerolipid metabolism	+	–	92.8250	0.9037
	1.3.8 Glycerophospholipid metabolism	+	–	94.3053	0.9288
	1.3.9 Primary bile acid biosynthesis	–	–	78.0995	0.0898
	1.3.10 Sphingolipid metabolism	+	+	72.0640	0.9527
	1.3.11 Steroid biosynthesis	+	–	121.0063	0.9227
	1.3.12 Steroid hormone biosynthesis	–	–	72.3171	0.7443
	1.3.13 Synthesis and degradation of ketone bodies	+	–	206.3421	0.6978
1.4 Nucleotide Metabolism	1.4.1 Purine metabolism	+	0	67.1810	0.9883
	1.4.2 Pyrimidine metabolism	–	+	55.9357	0.9737
	1.5.1 Alanine, aspartate and glutamate metabolism	–	–	23.4388	0.6249
	1.5.2 Arginine and proline metabolism	+	+	58.9064	0.8663
	1.5.3 Cysteine and methionine metabolism	–	+	77.7042	0.8262
	1.5.4 Glycine, serine and threonine metabolism	–	–	89.2756	0.8998
	1.5.5 Histidine metabolism	+	+	84.3671	0.9478
	1.5.6 Lysine degradation	+	+	47.0304	0.9288
	1.5.7 Phenylalanine metabolism	+	–	26.9976	0.2690
	1.5.8 Tryptophan metabolism	+	+	72.0211	0.9315

	1.5.9 Tyrosine metabolism	+	+	43.7772	0.6077
	1.5.10 Valine, leucine and isoleucine biosynthesis	+	–	66.2345	0.9153
	1.5.11 Valine, leucine and isoleucine degradation	+	+	97.1839	0.9329
1.6 Metabolism of Other Amino Acids	1.6.1 beta-Alanine metabolism	+	+	72.4806	0.8334
	1.6.2 Glutathione metabolism	+	–	112.5921	0.9762
	1.6.3 Selenoamino acid metabolism	+	+	46.0014	0.8317
	1.6.4 Taurine and hypotaurine metabolism	+	+	101.4887	0.9122
1.7 Glycan Biosynthesis and Metabolism	1.7.1 Glycosaminoglycan biosynthesis - chondroitin sulfate	+	–	91.4136	0.8830
	1.7.2 Glycosaminoglycan biosynthesis - heparan sulfate	–	+	103.0040	0.8980
	1.7.3 Glycosaminoglycan biosynthesis - keratan sulfate	+	+	53.9555	0.8702
	1.7.4 Glycosaminoglycan degradation	+	–	65.9137	0.9387
	1.7.5 Glycosphingolipid biosynthesis - ganglio series	+	+	91.0184	0.9251
	1.7.6 Glycosphingolipid biosynthesis - globo series	+	+	74.6927	0.9030
	1.7.7 Glycosphingolipid biosynthesis - lacto and neolacto series	+	–	71.8175	0.9842
	1.7.8 Glycosylphosphatidylinositol(GPI)-anchor biosynthesis	+	–	303.8882	0.9358
	1.7.9 N-Glycan biosynthesis	+	–	48.7764	0.9633
	1.7.10 O-Glycan biosynthesis	–	–	55.6061	0.7446
	1.7.11 O-Mannosyl glycan biosynthesis	–	+	67.7740	0.9492
	1.7.12 Other glycan degradation	+	+	47.3447	0.7879
1.8 Metabolism of Cofactors and Vitamins	1.8.1 Folate biosynthesis	–	+	64.9525	0.3228
	1.8.2 Nicotinate and nicotinamide metabolism	+	+	66.1624	0.7448
	1.8.3 One carbon pool by folate	–	+	56.5752	0.1912
	1.8.4 Pantothenate and CoA biosynthesis	+	–	78.9686	0.8218
	1.8.5 Porphyrin and chlorophyll metabolism	–	+	97.3036	0.8864
	1.8.6 Retinol metabolism	+	–	95.4645	0.8387

	1.8.7 Riboflavin metabolism	+	+	107.4750	-0.0345
	1.8.8 Vitamin B6 metabolism	+	+	198.9522	0.1267
1.11 Xenobiotics Biodegradation and Metabolism	1.11.1 Drug metabolism - cytochrome P450	+	+	88.5239	0.8412
	1.11.2 Drug metabolism - other enzymes	+	+	131.1170	0.9440
	1.11.3 Metabolism of xenobiotics by cytochrome P450	–	–	72.4936	0.9573

2. Genetic Information Processing

KEGG pathway subcategory	The secondary pathways	Impact direction		Impact values	
		DIA direction	gradient direction	DIA average value	total effect
2.1 Transcription	2.1.1 Basal transcription factors	–	+	30.2114	0.9226
	2.1.2 RNA polymerase	+	–	42.3286	0.9616
	2.1.3 Spliceosome	–	+	41.7172	0.9848
2.2 Translation	2.2.1 Aminoacyl-tRNA biosynthesis	+	–	63.8779	0.7486
	2.2.2 mRNA surveillance pathway	–	+	78.4853	0.9338
	2.2.3 Ribosome	–	+	66.2014	0.5327
	2.2.4 Ribosome biogenesis in eukaryotes	–	–	43.4695	0.9916
	2.2.5 RNA transport	–	–	51.6779	0.8754
2.3 Folding, Sorting and Degradation	2.3.1 Proteasome	+	–	33.1836	0.7362
	2.3.2 Protein export	+	+	86.6874	0.4953
	2.3.3 Protein processing in endoplasmic reticulum	+	–	66.7127	0.9709
	2.3.4 RNA degradation	–	+	46.5263	0.9096
	2.3.5 SNARE interactions in vesicular transport	+	+	53.0798	0.9287
	2.3.6 Sulfur relay system	–	–	76.7757	0.8276
	2.3.7 Ubiquitin mediated proteolysis	–	–	52.0947	0.9878

2.4 Replication and Repair	2.4.1 Base excision repair	–	+	47.4026	0.8487
	2.4.2 DNA replication	–	–	75.7622	0.9381
	2.4.3 Homologous recombination	–	+	90.0717	0.9818
	2.4.4 Mismatch repair	–	–	49.3064	0.8685
	2.4.5 Non-homologous end-joining	+	+	69.2194	0.7326
	2.4.6 Nucleotide excision repair	–	–	52.4301	0.9418

3. Environmental Information Processing

KEGG pathway subcategory	The secondary pathways	Impact direction		Impact values	
		DIA direction	gradient direction	DIA average value	total effect
3.2 Signal Transduction	3.2.1 Calcium signaling pathway	+	+	82.8815	0.9915
	3.2.2 ErbB signaling pathway	+	+	70.4900	0.9897
	3.2.3 Hedgehog signaling pathway	+	+	132.6695	0.9773
	3.2.4 Jak-STAT signaling pathway	+	+	103.4910	0.9920
	3.2.5 MAPK signaling pathway	–	+	71.8846	0.9932
	3.2.6 mTOR signaling pathway	–	–	48.6561	0.9396
	3.2.7 Notch signaling pathway	–	+	73.6045	0.9798
	3.2.8 Phosphatidylinositol signaling system	+	+	65.9386	0.9886
	3.2.9 TGF-beta signaling pathway	+	+	110.0261	0.9236
	3.2.10 VEGF signaling pathway	+	–	82.8140	0.9364
	3.2.11 Wnt signaling pathway	–	+	74.7935	0.9809
3.3 Signaling Molecules and Interaction	3.3.1 Cell adhesion molecules (CAMs)	–	+	112.5810	0.9817
	3.3.2 Cytokine-cytokine receptor interaction	+	+	90.5058	0.9653
	3.3.3 ECM-receptor interaction	+	–	110.5346	0.9412

	3.3.4 Neuroactive ligand-receptor interaction	+		170.7323	0.9503

4. Cellular Processes

KEGG pathway subcategory	The secondary pathways	Impact direction		Impact values	
		DIA direction	gradient direction	DIA average value	total effect
4.1 Transport and Catabolism	4.1.1 Endocytosis	–	–	58.3346	0.9778
	4.1.2 Lysosome	–	+	62.2135	0.9676
	4.1.3 Peroxisome	+	–	115.5367	0.9930
	4.1.4 Phagosome	+	–	115.4442	0.9338
	4.1.5 Regulation of autophagy	+	–	68.1809	0.6753
4.3 Cell Growth and Death	4.3.1 Apoptosis	+	–	64.5272	0.9745
	4.3.2 Cell cycle	–	+	76.5937	0.9885
	4.3.3 Oocyte meiosis	–	–	70.2151	0.9755
	4.3.4 p53 signaling pathway	+	+	87.5647	0.9571
4.4 Cell Communication	4.4.1 Adherens junction	+	–	50.3326	0.9851
	4.4.2 Focal adhesion	+	–	73.4476	0.9804
	4.4.3 Gap junction	–	–	82.8339	0.9902
	4.4.4 Tight junction	+	+	88.8610	0.9881

5. Organismal Systems

KEGG pathway subcategory	The secondary pathways	Impact direction		Impact values	
		DIA direction	gradient direction	DIA average value	total effect
5.1 Immune System	5.1.1 Antigen processing and presentation	–	+	170.7323	0.9632
	5.1.2 B cell receptor signaling pathway	+	–	75.4511	0.9893
	5.1.3 Chemokine signaling pathway	+	–	76.3412	0.9933
	5.1.4 Complement and coagulation cascades	+	+	97.7197	0.9432
	5.1.5 Cytosolic DNA-sensing pathway	+	–	46.6657	0.8947
	5.1.6 Fc epsilon RI signaling pathway	+	–	110.7868	0.9957
	5.1.7 Fc gamma R-mediated phagocytosis	–	–	82.6388	0.9860
	5.1.8 Hematopoietic cell lineage	+	+	117.0012	0.9690
	5.1.9 Intestinal immune network for IgA production	–	–	100.0108	0.9950
	5.1.10 Leukocyte transendothelial migration	+	–	70.3332	0.9897
	5.1.11 Natural killer cell mediated cytotoxicity	+	–	92.6672	0.9789
	5.1.12 NOD-like receptor signaling pathway	+	–	73.1123	0.9872
	5.1.13 RIG-I-like receptor signaling pathway	+	–	68.4491	0.9375
	5.1.14 T cell receptor signaling pathway	+	–	70.1399	0.9846

	5.1.15 Toll-like receptor signaling pathway	+	–	74.8328	0.9946
5.2 Endocrine System	5.2.1 Adipocytokine signaling pathway	–	–	127.6228	0.9927
	5.2.2 GnRH signaling pathway	+	–	100.5363	0.9836
	5.2.3 Insulin signaling pathway	–	+	70.6464	0.9841
	5.2.4 Melanogenesis	+	+	72.5094	0.9226
	5.2.5 PPAR signaling pathway	+	–	254.6453	0.9463
	5.2.6 Progesterone-mediated oocyte maturation	+	+	65.6063	0.9860
5.3 Circulatory System	5.3.1 Cardiac muscle contraction	+	0	59.3131	0.9358
	5.3.2 Vascular smooth muscle contraction	+	+	66.8803	0.9543
5.4 Digestive System	5.4.1 Bile secretion	+	+	114.2395	0.9839
	5.4.2 Carbohydrate digestion and absorption	–	–	58.0398	0.8228
	5.4.3 Fat digestion and absorption	+	+	103.4787	0.9862
	5.4.4 Gastric acid secretion	–	+	77.9348	0.9786
	5.4.5 Mineral absorption	–	+	64.9307	0.9327
	5.4.6 Pancreatic secretion	–	+	86.4339	0.9777
	5.4.7 Protein digestion and absorption	+	–	80.6882	0.8386
	5.4.8 Salivary secretion	–	+	99.0573	0.9949
	5.4.9 Vitamin digestion and absorption	–	–	61.7875	0.6045
5.5 Excretory System	5.5.1 Aldosterone-regulated sodium reabsorption	–	–	74.8391	0.9319
	5.5.2 Collecting duct acid secretion	+	–	101.2018	0.8759
	5.5.3 Endocrine and other factor-regulated calcium reabsorption	–	–	101.9189	0.9776
	5.5.4 Proximal tubule bicarbonate reclamation	–	–	215.9654	0.9784
	5.5.5 Vasopressin-regulated water reabsorption	–	+	34.9397	0.8259
5.6 Nervous System	5.6.1 Glutamatergic synapse	+	+	84.0151	0.9965

	5.6.2 Long-term depression	+	+	84.1107	0.9935
	5.6.3 Long-term potentiation	+	+	78.3053	0.9990
	5.6.4 Neurotrophin signaling pathway	+	+	61.5298	0.9936
5.8 Development	5.8.1 Axon guidance	+	+	95.1003	0.9827
	5.8.2 Dorso-ventral axis formation	+	–	99.3535	0.7175
	5.8.3 Osteoclast differentiation	+	+	69.3424	0.9777