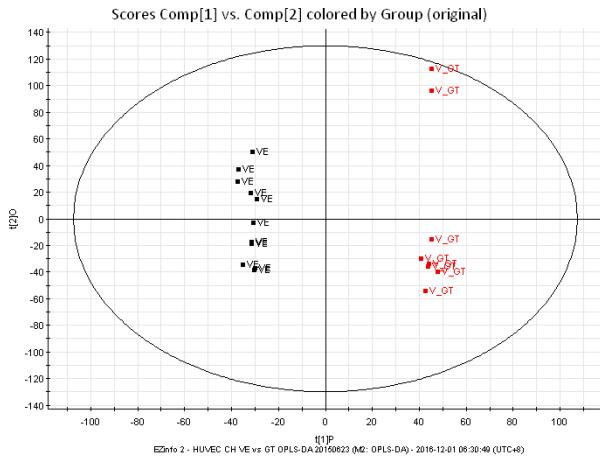


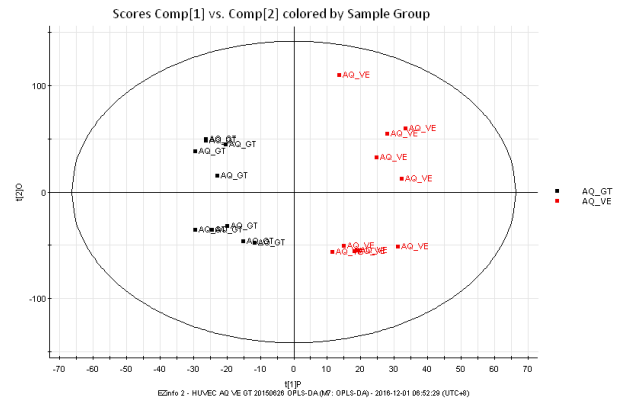
Supporting Information

Fig. S1. Metabolomics analyzed by OPLS-DA. Diagrams show the VEGF treatment groups can be differentiated with respect to the treatment: (a) green tea extract in organic fraction and (b) aqueous fraction; (c) EGCG in organic fraction and (d) aqueous fraction; (e) M1 in organic fraction and (f) aqueous fraction; (g) M2 in organic fraction and (h) aqueous fraction; and (i) bevacizumab in organic fraction and (j) aqueous fraction.

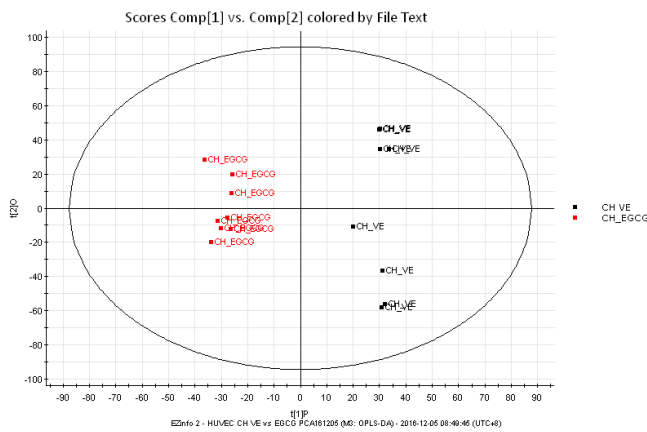
(a)



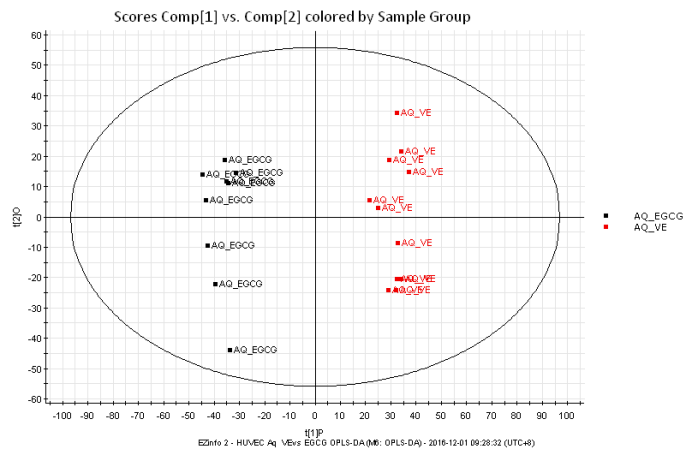
(b)



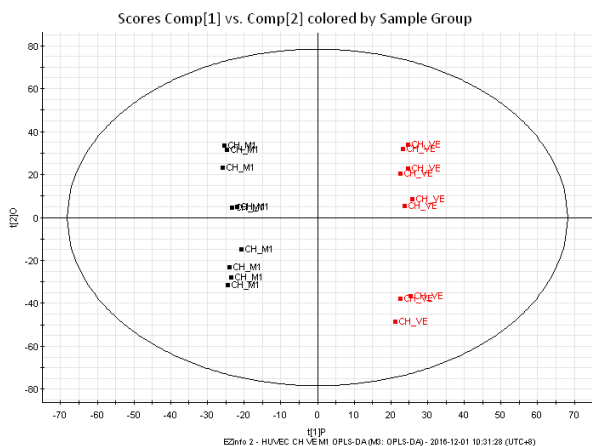
(c)



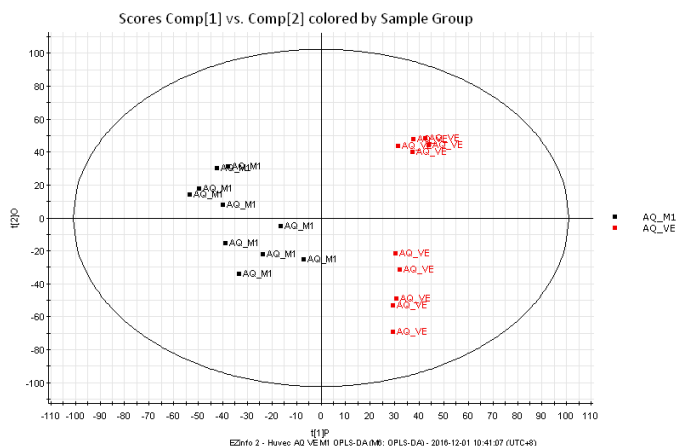
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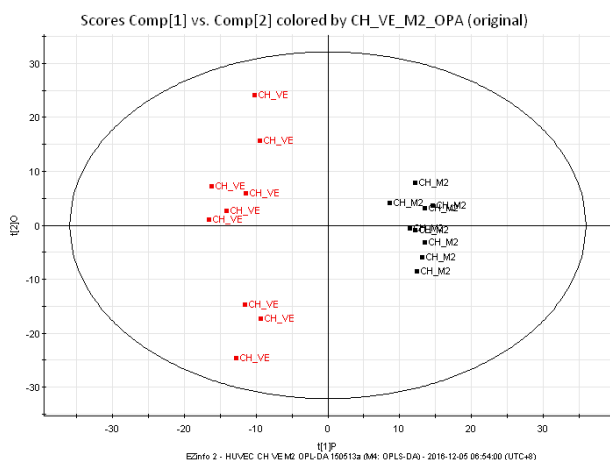
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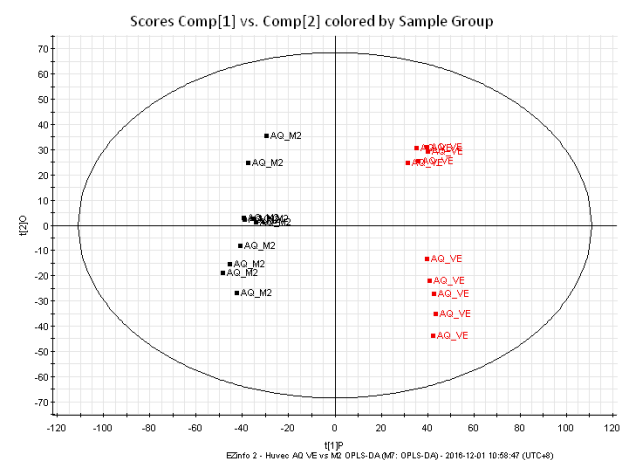
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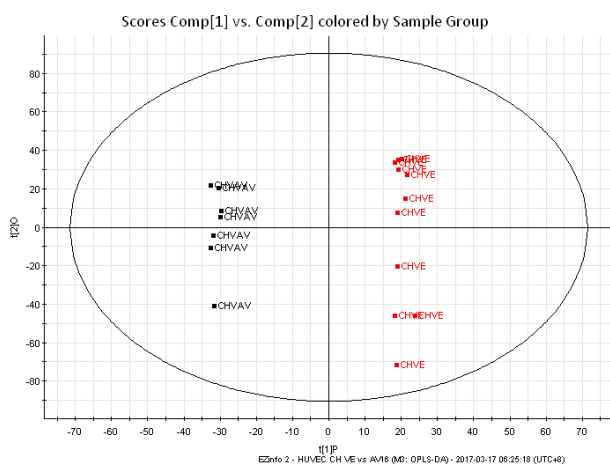
(g)



(h)



(i)



(j)

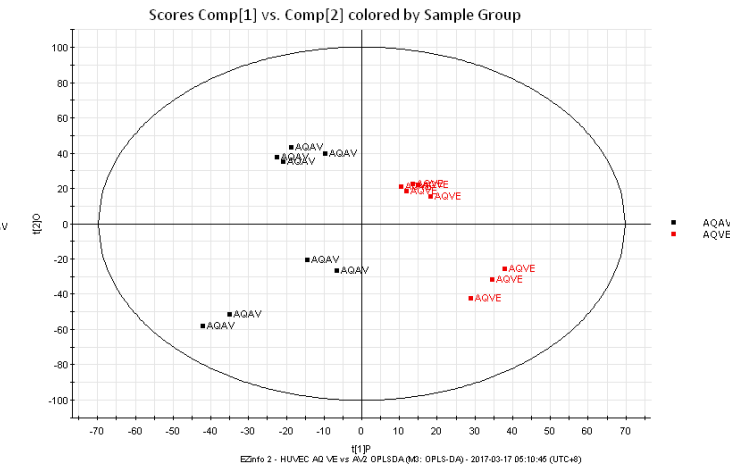
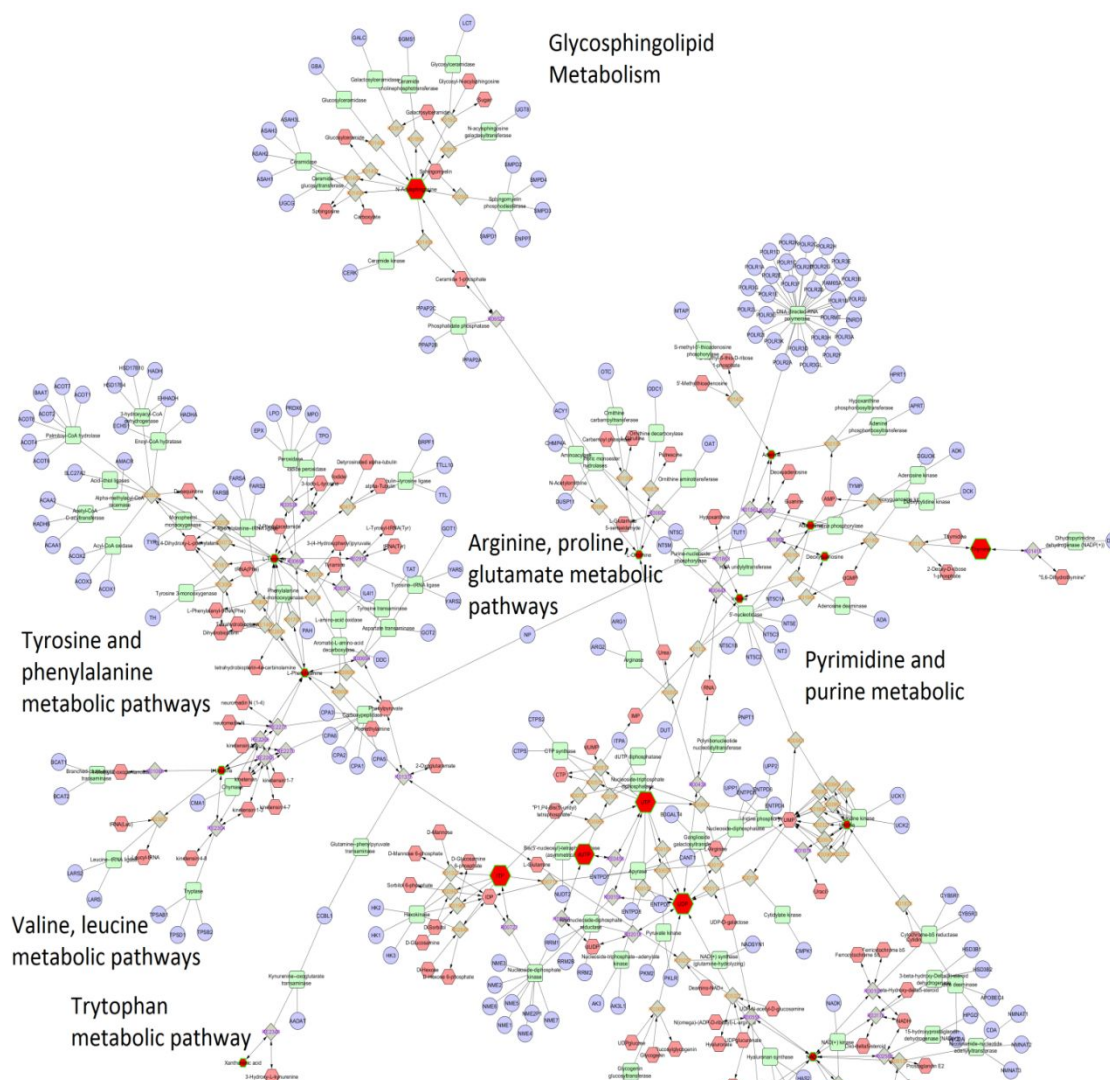
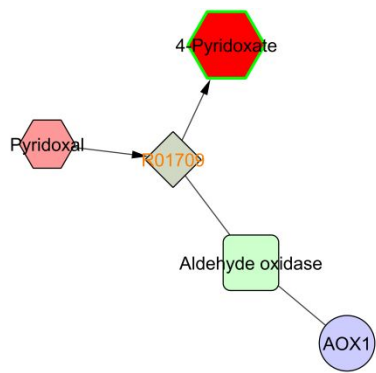


Fig. S2. Significant pathways from Metaboanalyst are verified by Metascope following GTE treatment on VEGF induced HUVEC. Diagrams show the affected (a) pyrimidine and purine metabolic pathways, and their interconnected amino acids and glycosphingolipid pathways; (b) vitamin B6; (c) methionine and cysteine; and (d) pantothenic acid metabolic pathways. Large hexagon indicates highly expressed. Small hexagon indicates under expressed.

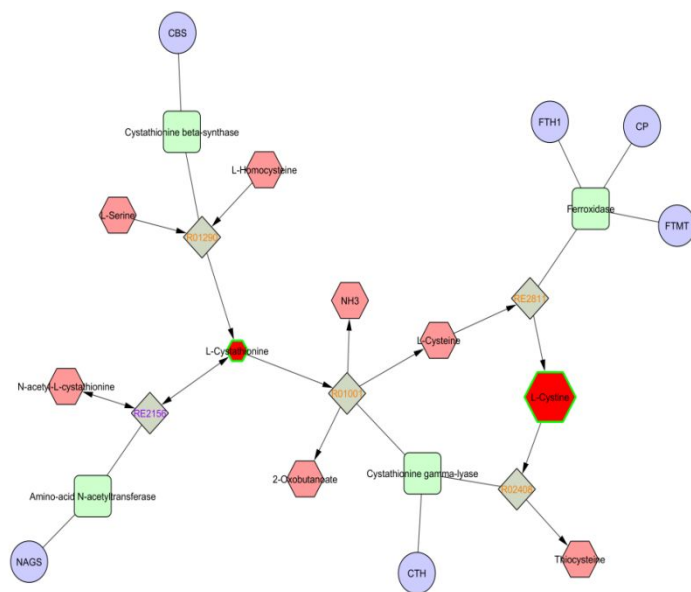
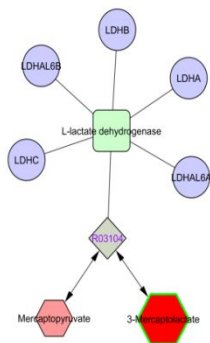
(a)



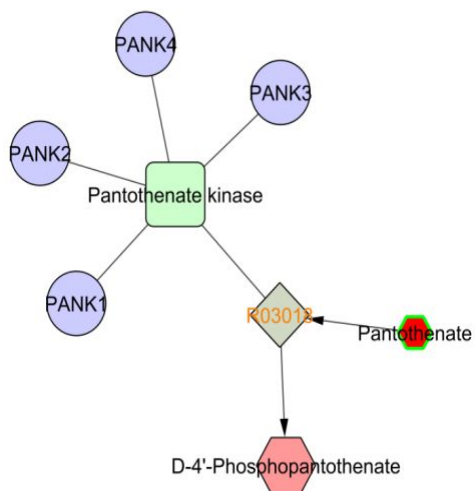
(b)



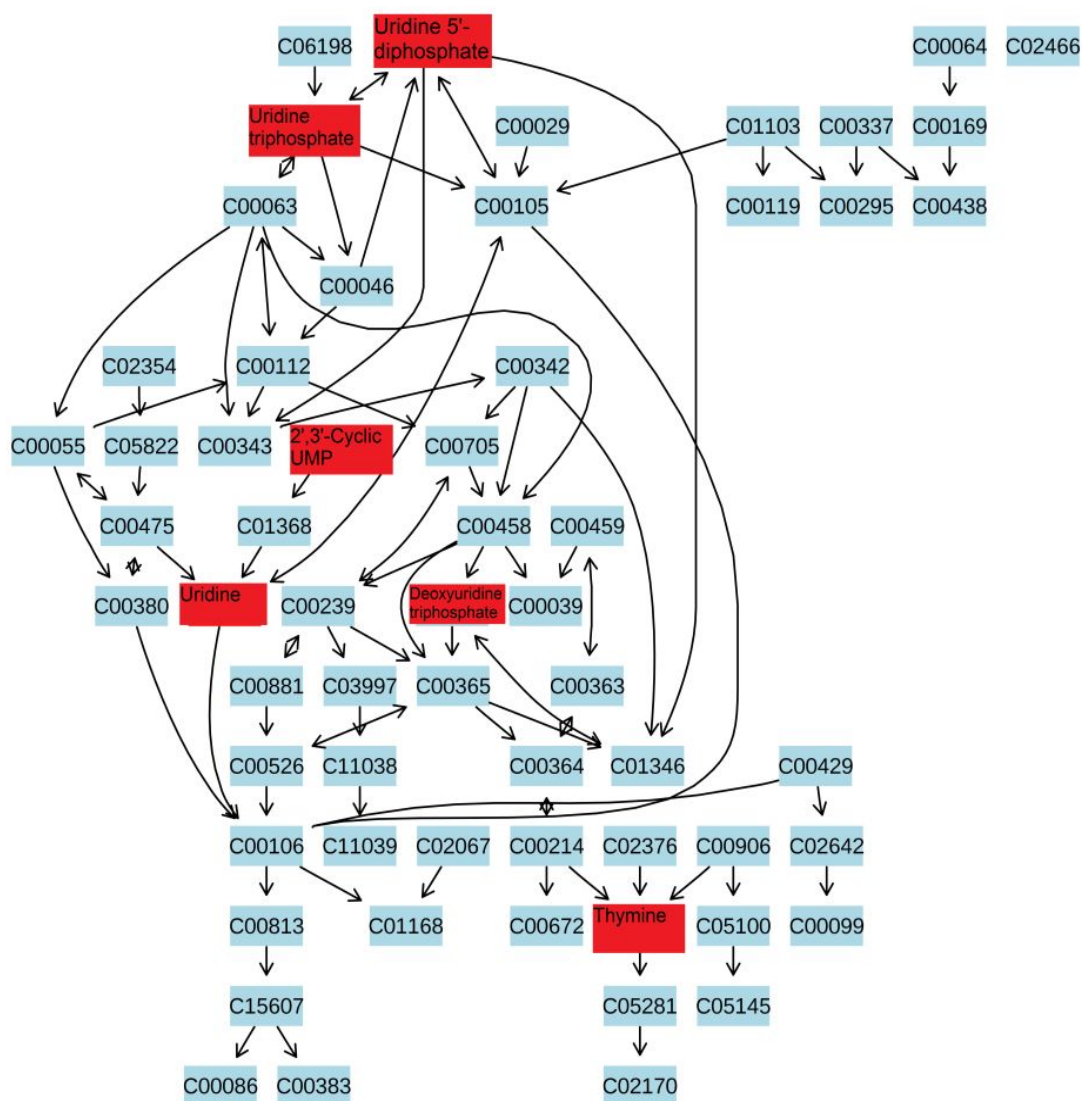
(c)



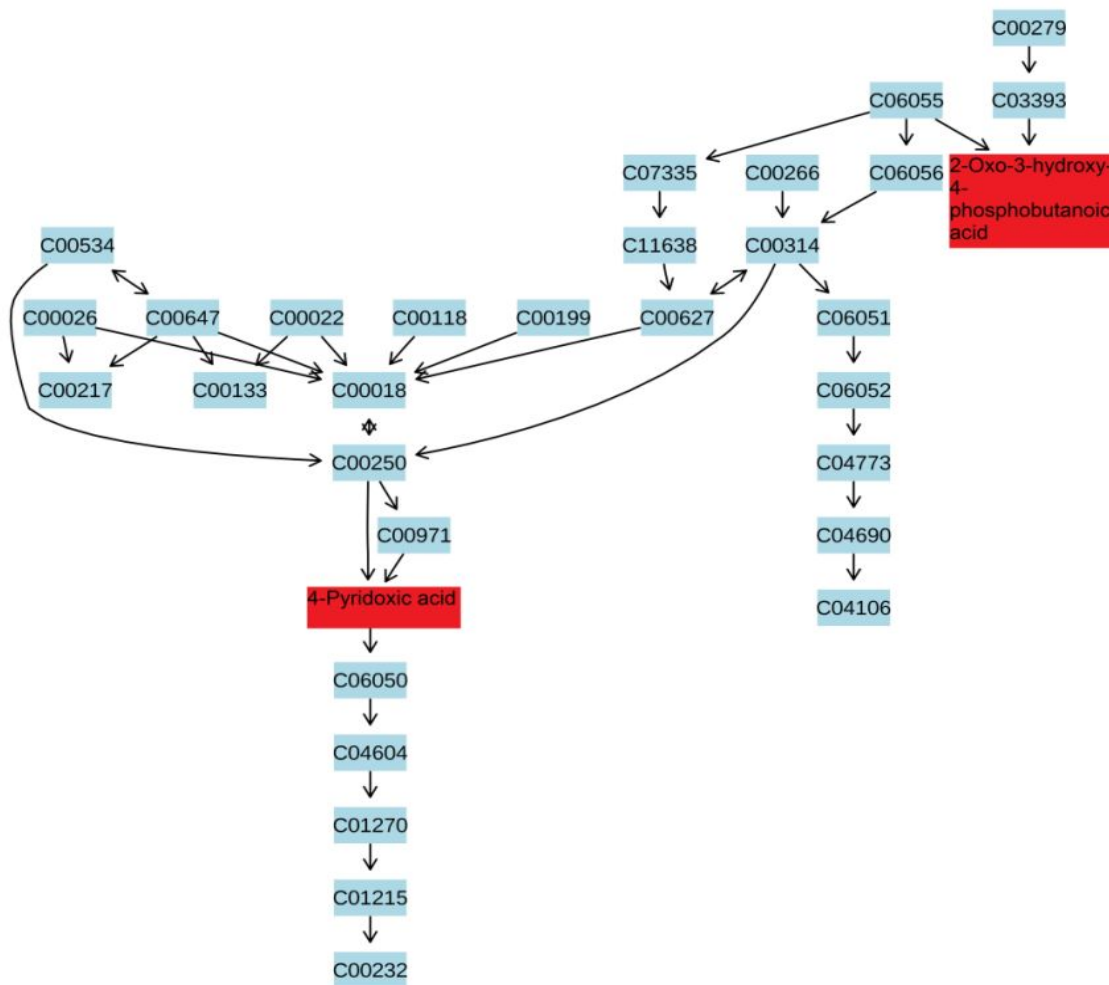
(d)



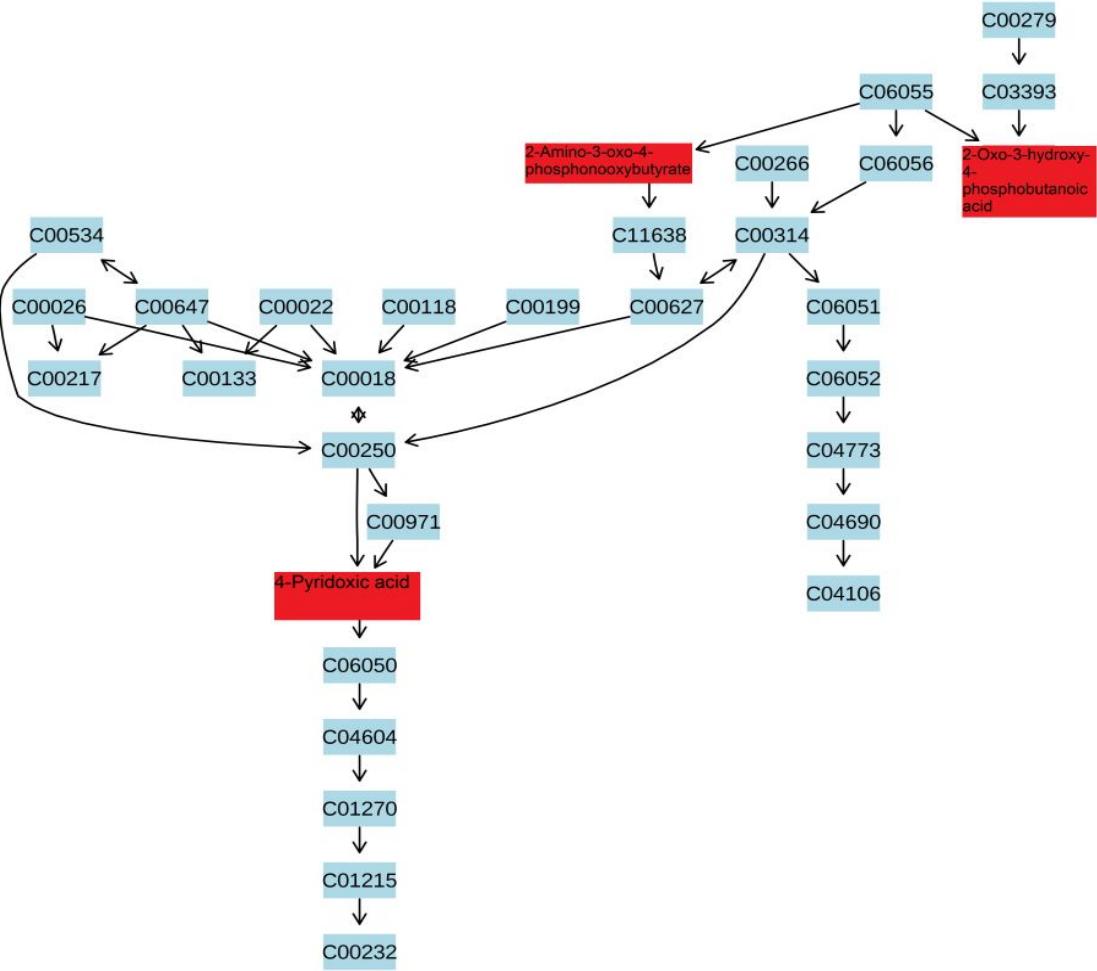
(b)



(c)



(d)



(e)

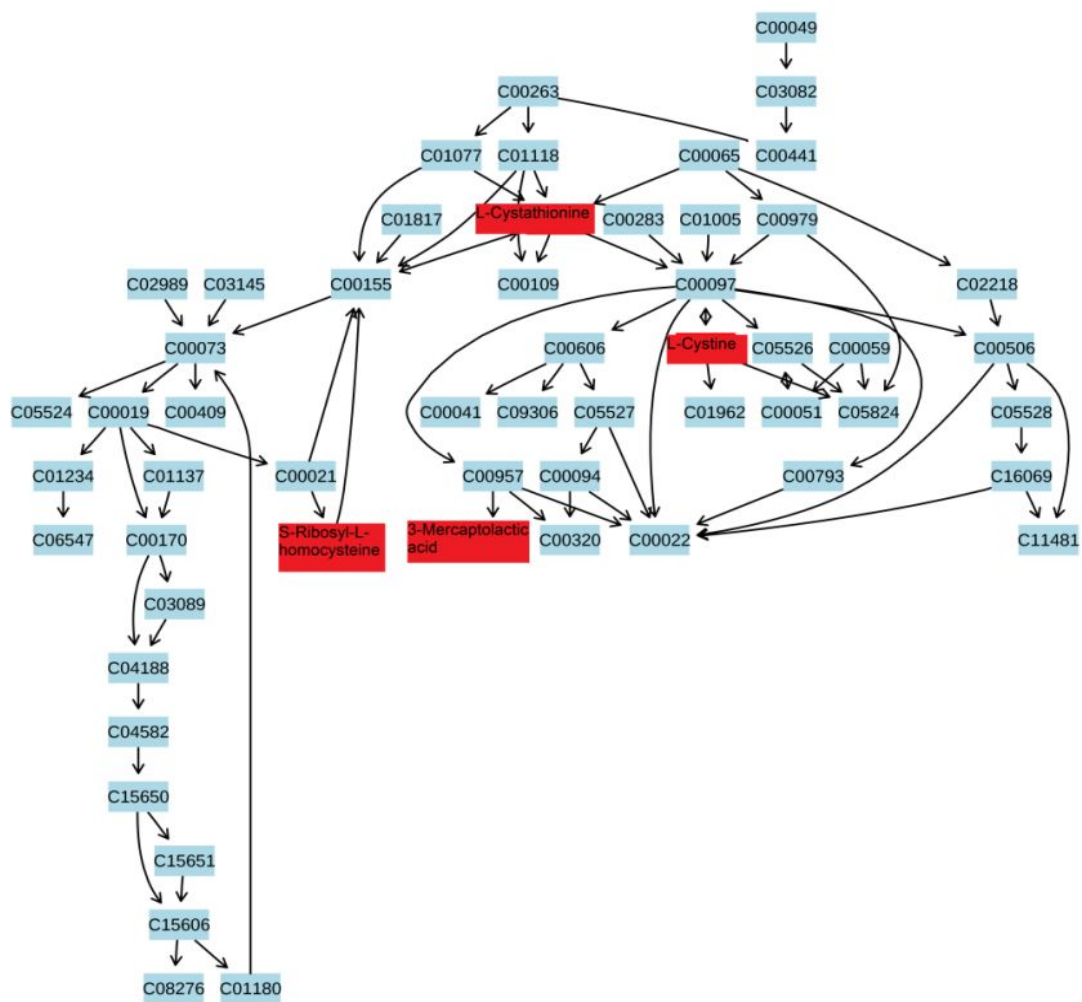
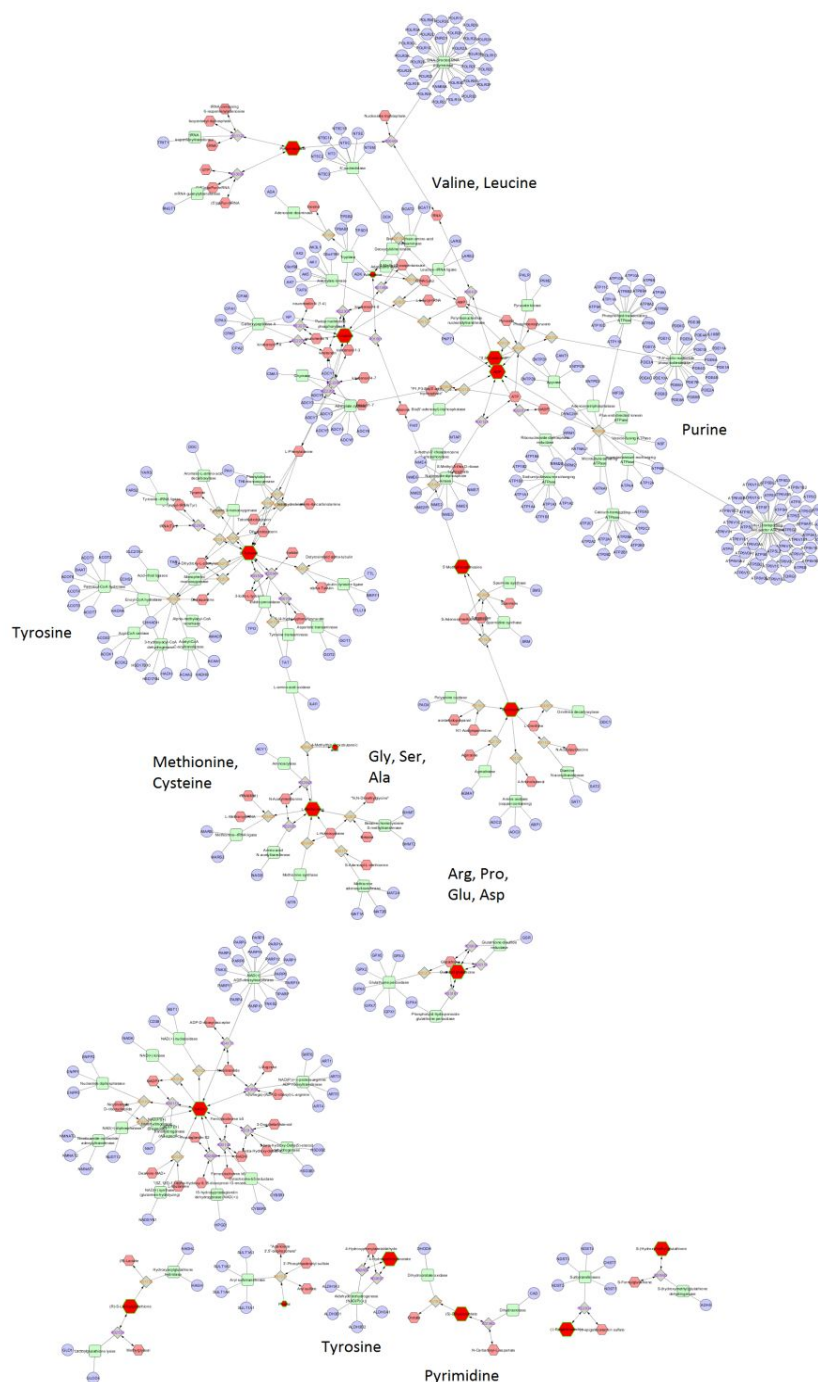
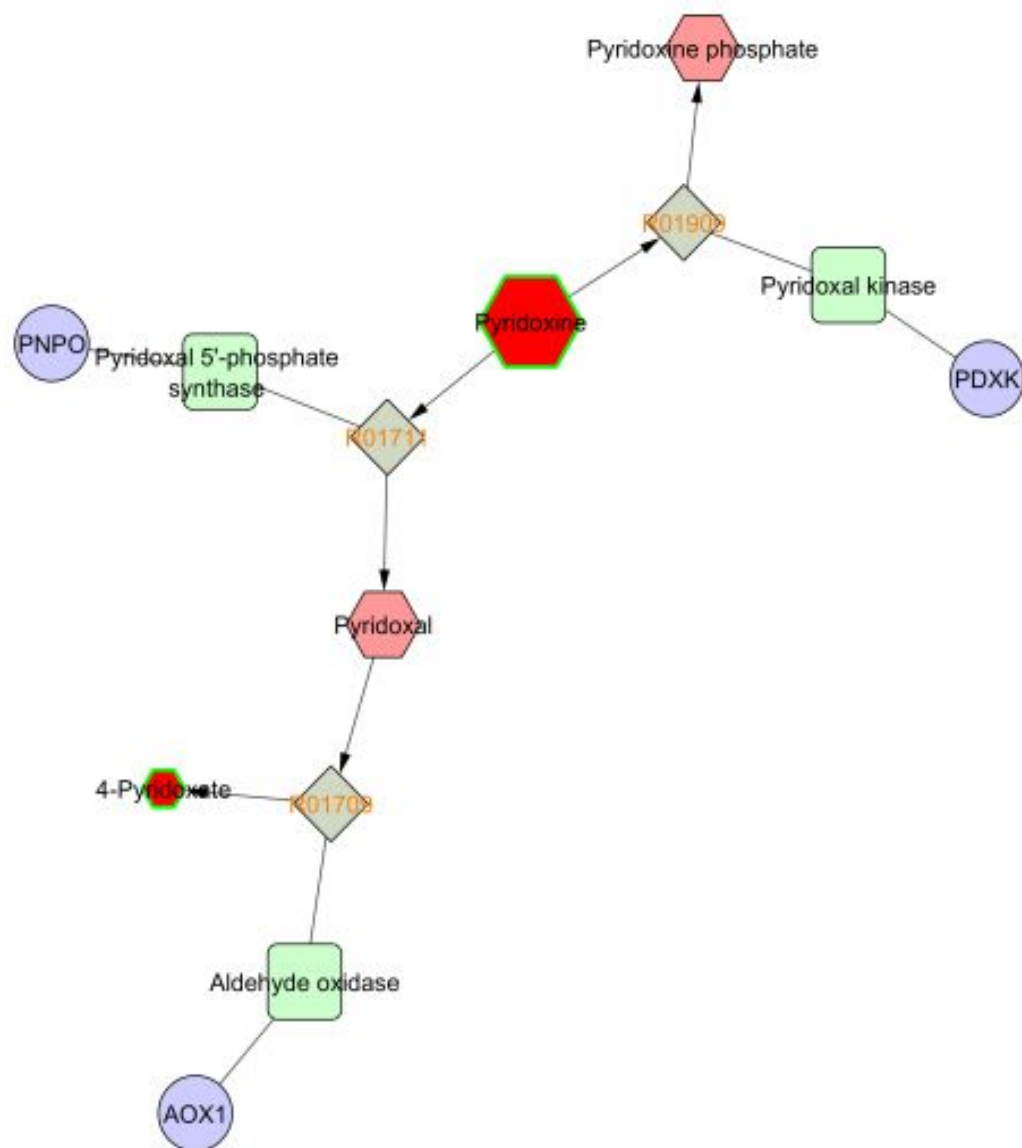


Fig. S4. Significant pathways from Metaboanalyst were verified by Metascape following EGCG treatment on VEGF induced HUVEC. Diagrams show the affected (a) amino acids metabolic pathways; (b) vitamin B6, (c) tyrosine, and (d) valine and leucine metabolic pathways. Large hexagon indicates highly expressed. Small hexagon indicates under expressed.

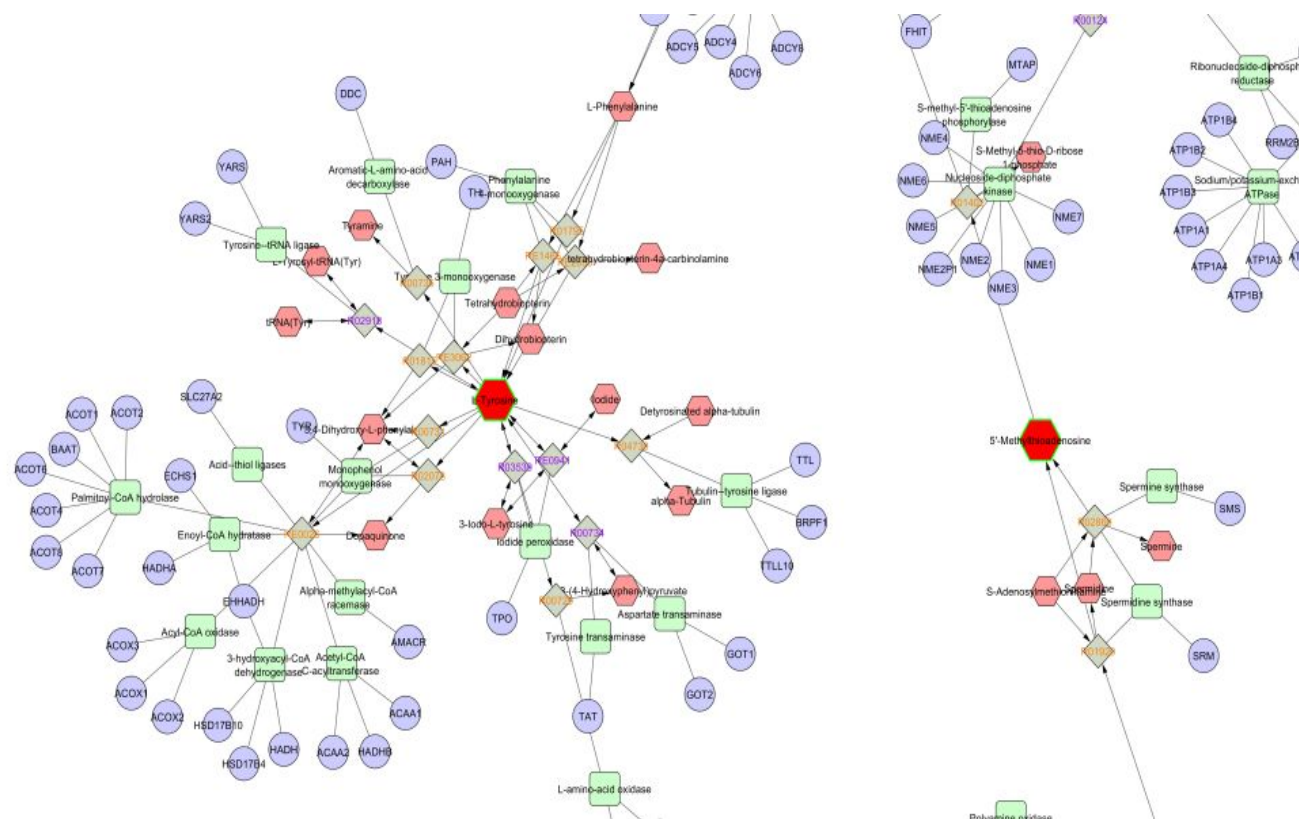
(a)



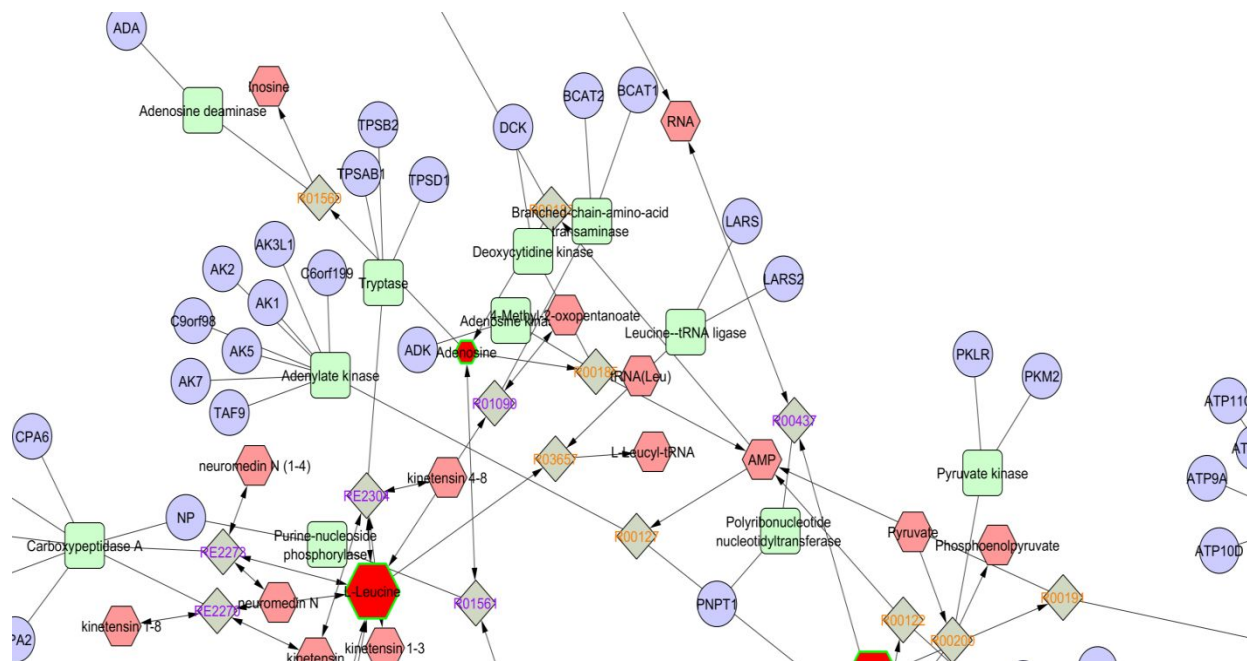
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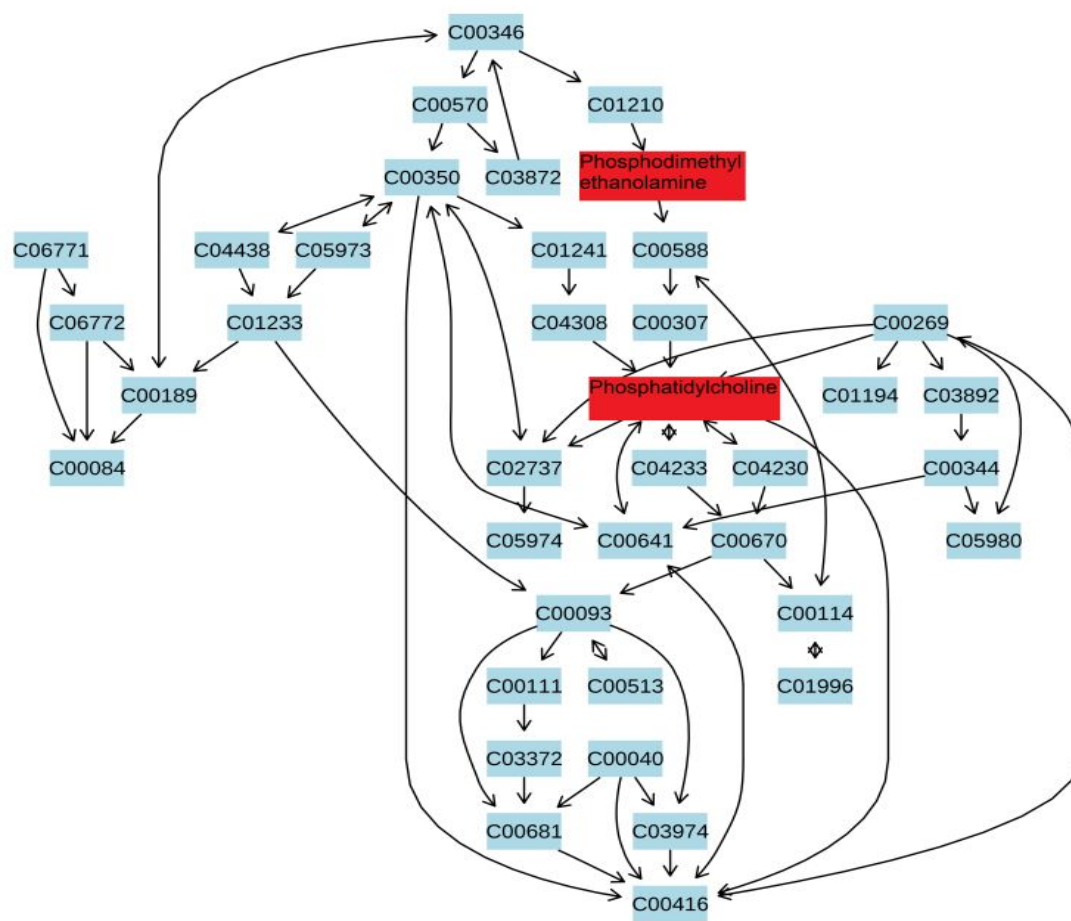
(c)



(d)



(b)



(c)

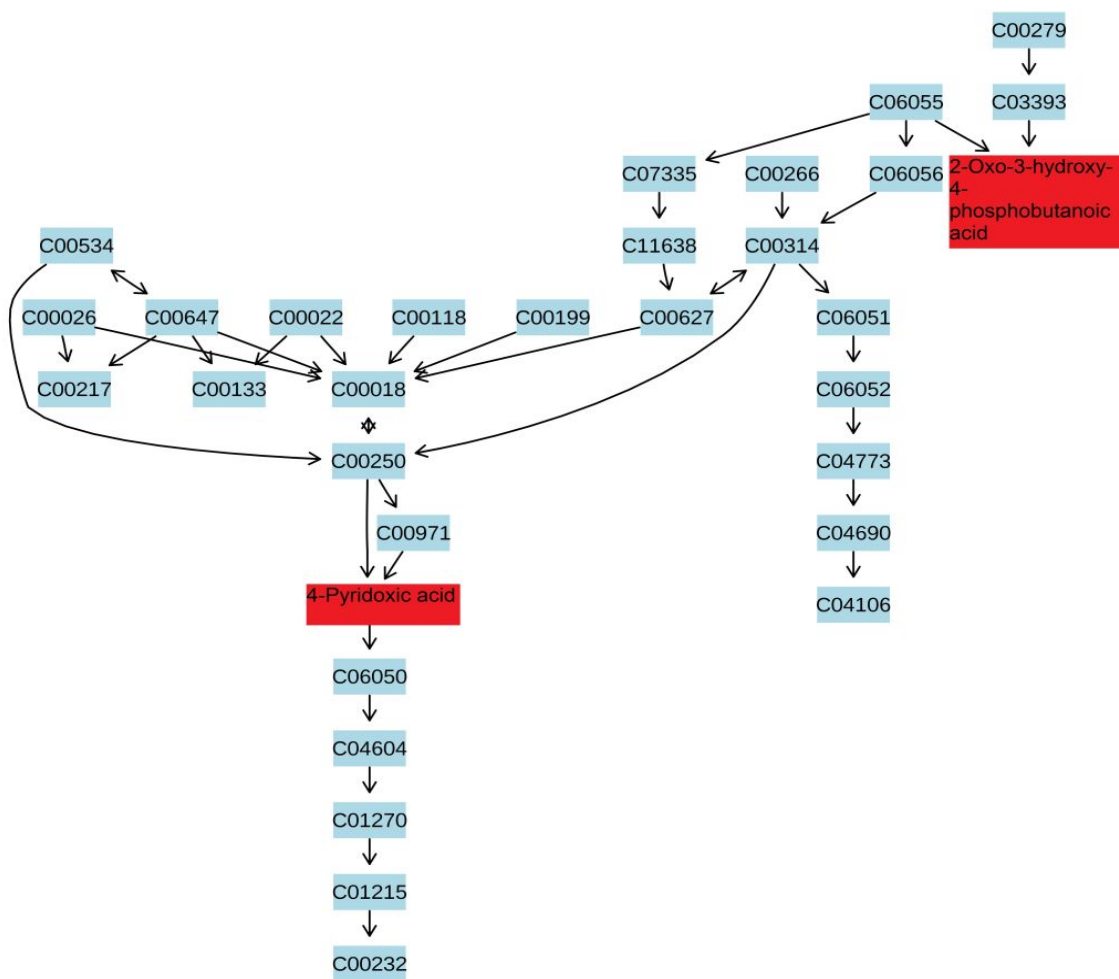
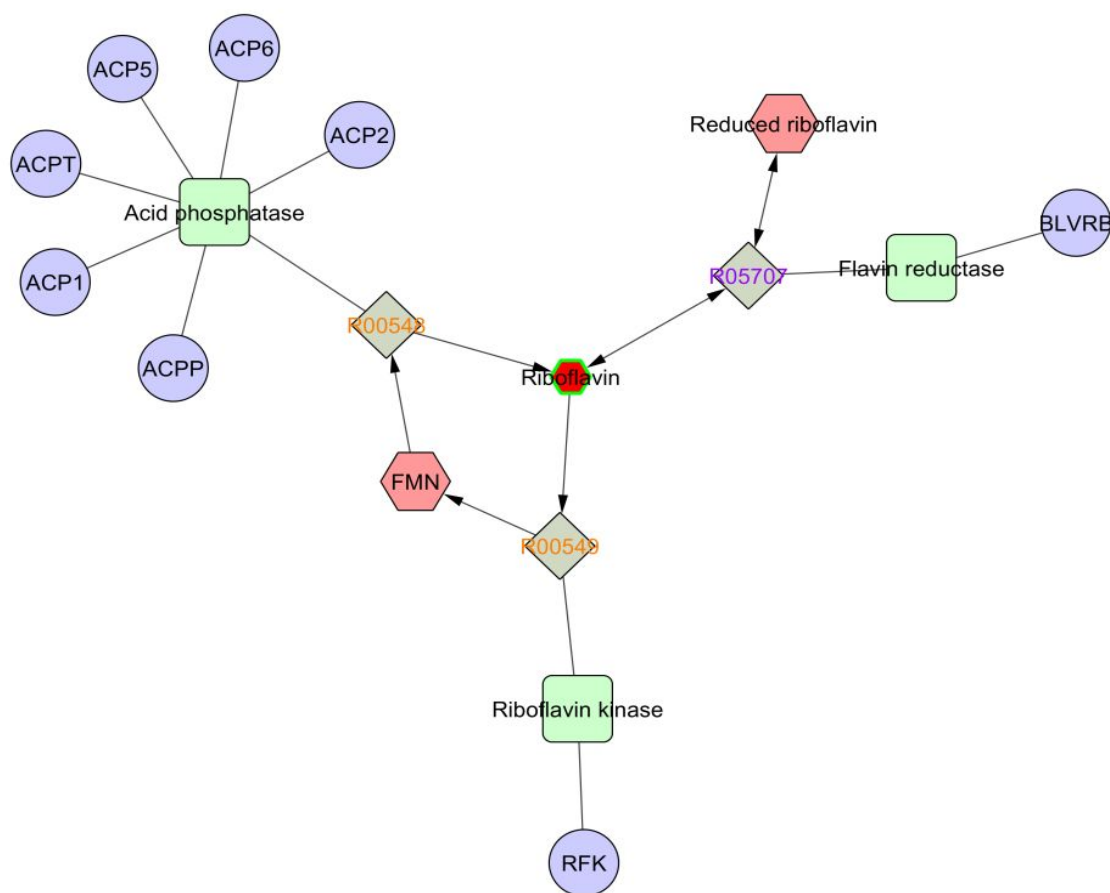


Fig. S6. Significant pathways from Metaboanalyst were verified by Metascape following M1 treatment on VEGF induced HUVEC. Diagrams show the affected (a) riboflavin metabolism, and (b) pantothenic acid and CoA biosynthesis pathways. Large hexagon indicates highly expressed. Small hexagon indicates under expressed.

(a)



(b)

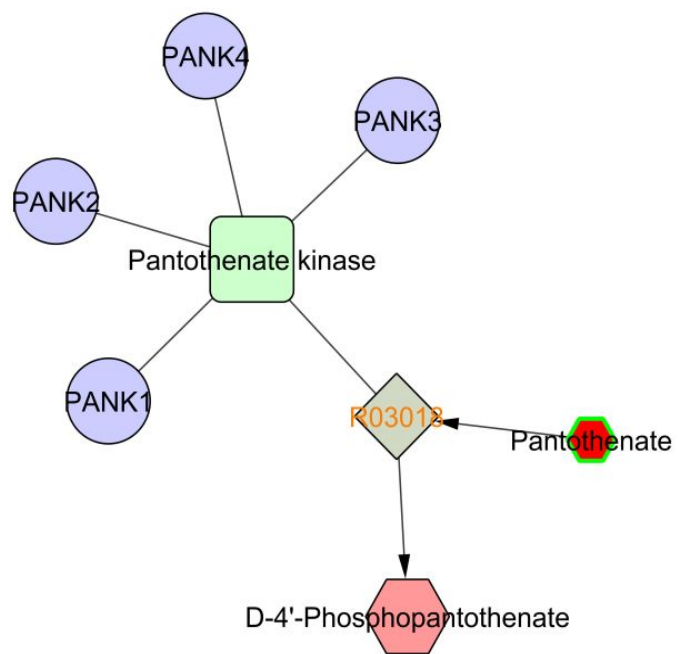
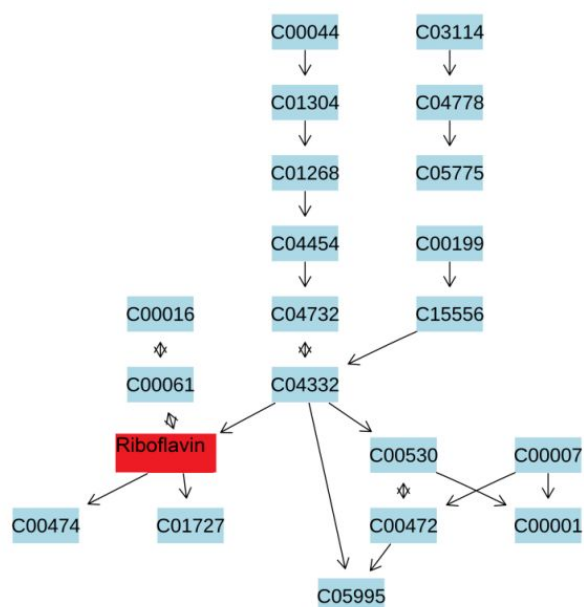
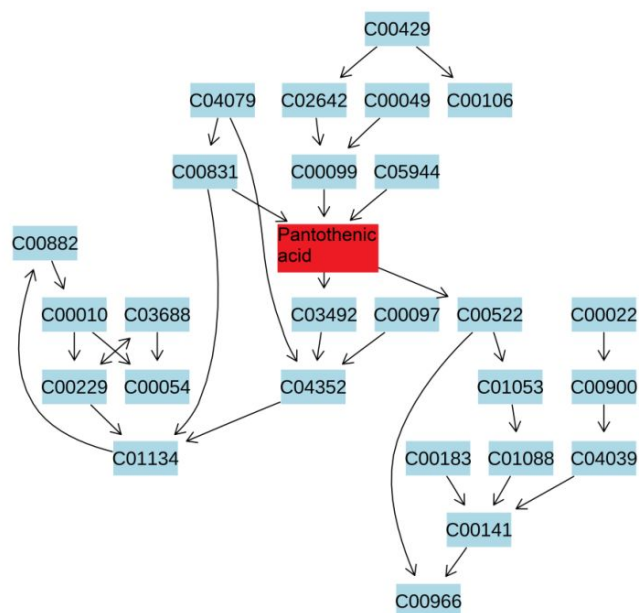


Fig. S7. Topology of metabolites in different pathways analyzed by Metaboanalyst following M1 treatment. Diagrams show the affected (a) riboflavin metabolism, (b) pantothenic acid biosynthesis, (c) phosphatidylethanolamine pathways. Metabolites (labeled in red) occupy in different key positions of the pathways.

(a)



(b)



(c)

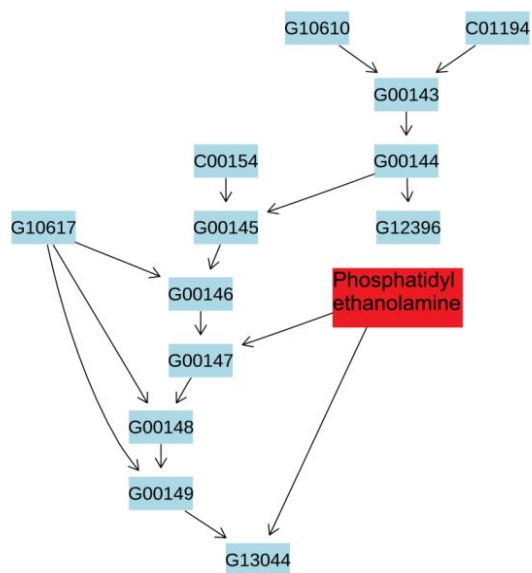


Fig. S8. Significant pathways from Metaboanalyst were verified by Metascape following M2 treatment on VEGF induced HUVEC. Diagram shows the affected (a) pantothenic acid metabolism pathway. Large hexagon indicates highly expressed. Small hexagon indicates under expressed.

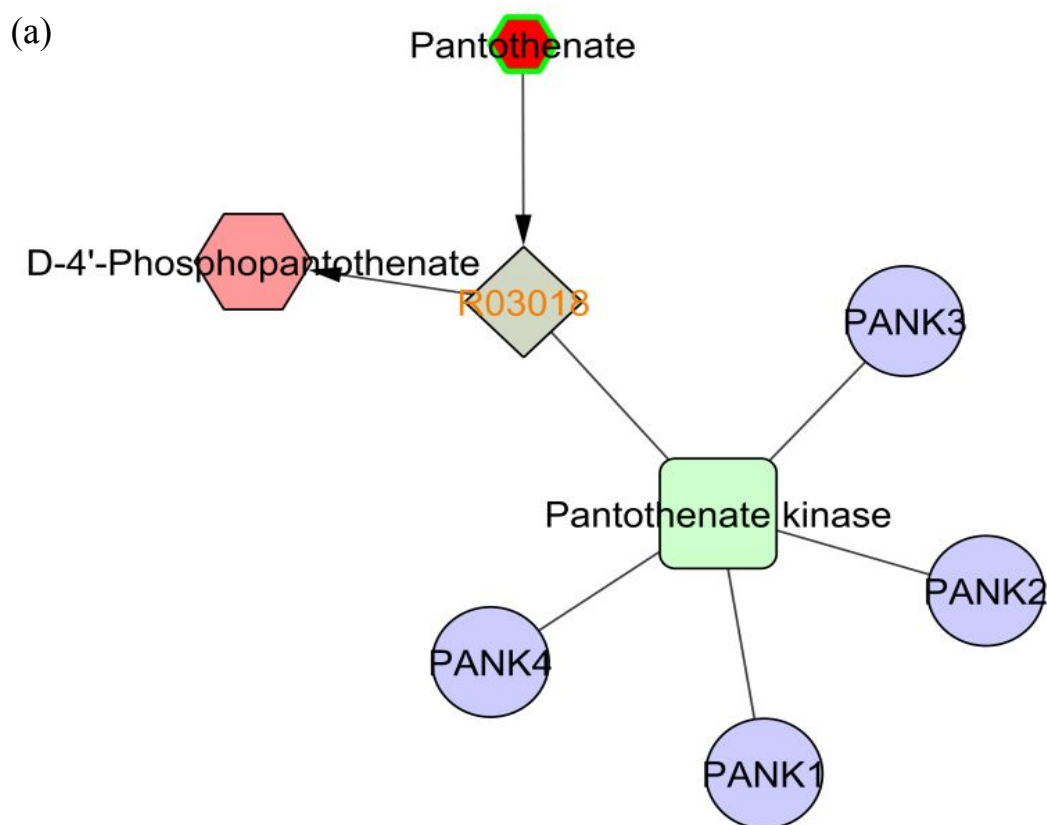


Fig. S9. Topology of metabolites in different pathways analyzed by Metaboanalyst following M2 treatment. Diagram shows the affected pantothenate and CoA biosynthesis pathway. Metabolites (labeled in red) occupy in different key positions of the pathways.

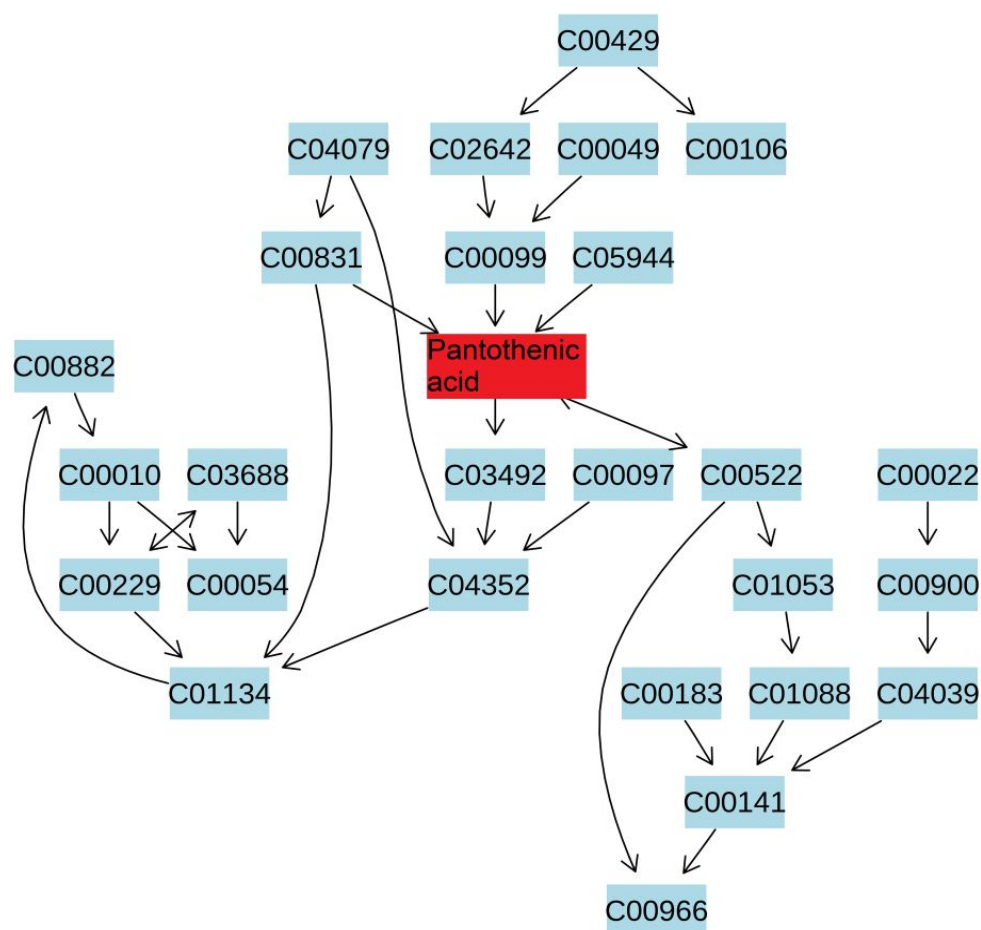
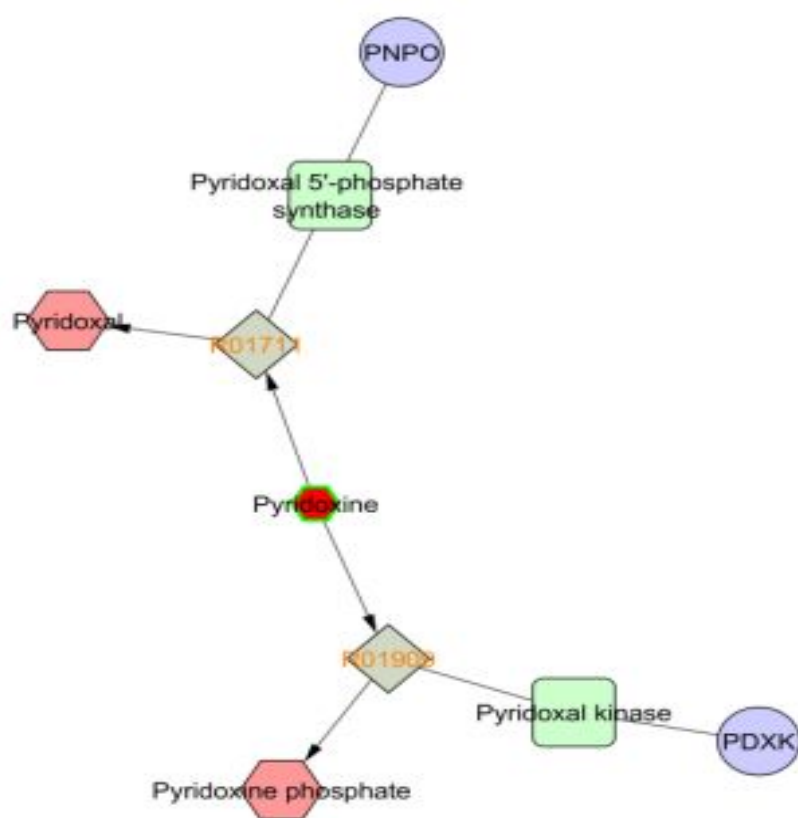


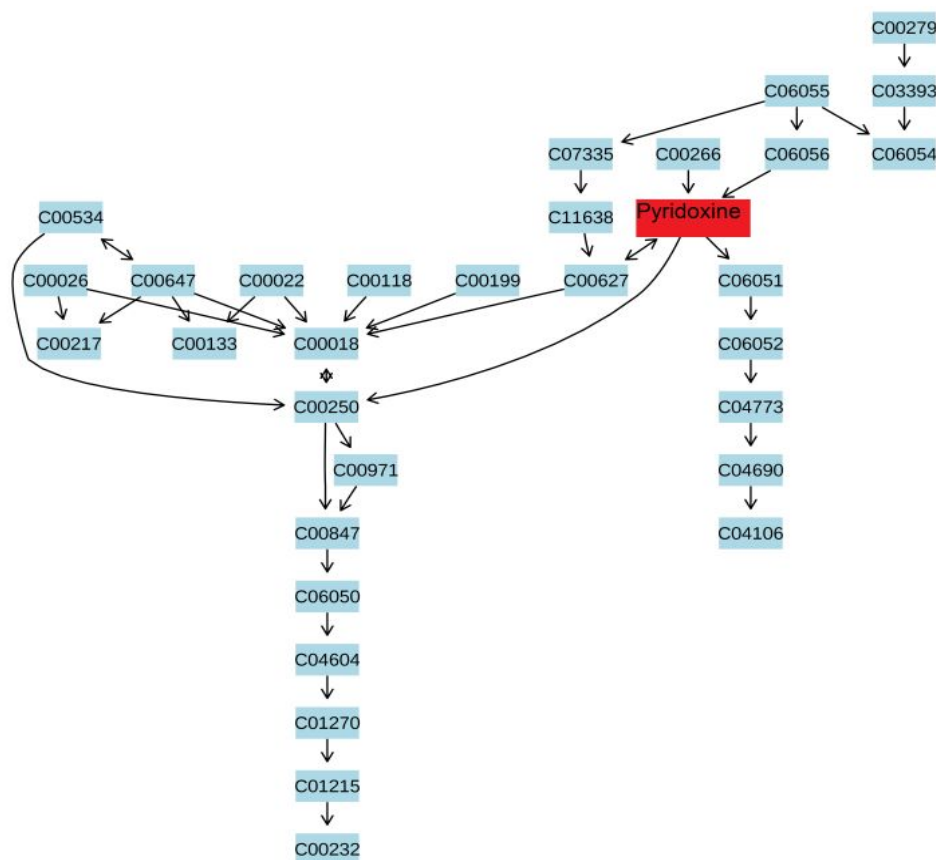
Fig. 10. Significant pathways from Metaboanalyst were verified by Metscape following bevacizumab treatment on VEGF induced HUVEC. Diagrams show the affected (a) vitamin B6 metabolism biosynthesis, and (b) tyrosine metabolism pathways. Large hexagon indicates highly expressed. Small hexagon indicates under expressed.

(a)



[illegible]

Fig. S11. Topology of metabolites in different pathways analyzed by Metaboanalyst following bevacizumab treatment. Diagrams show the affected (a) vitamin B6 metabolism, and (b) phenylalanine, and tyrosine and tryptophan biosynthesis pathways. Metabolites (labeled in red) occupy in different key positions of the pathways.



(b)

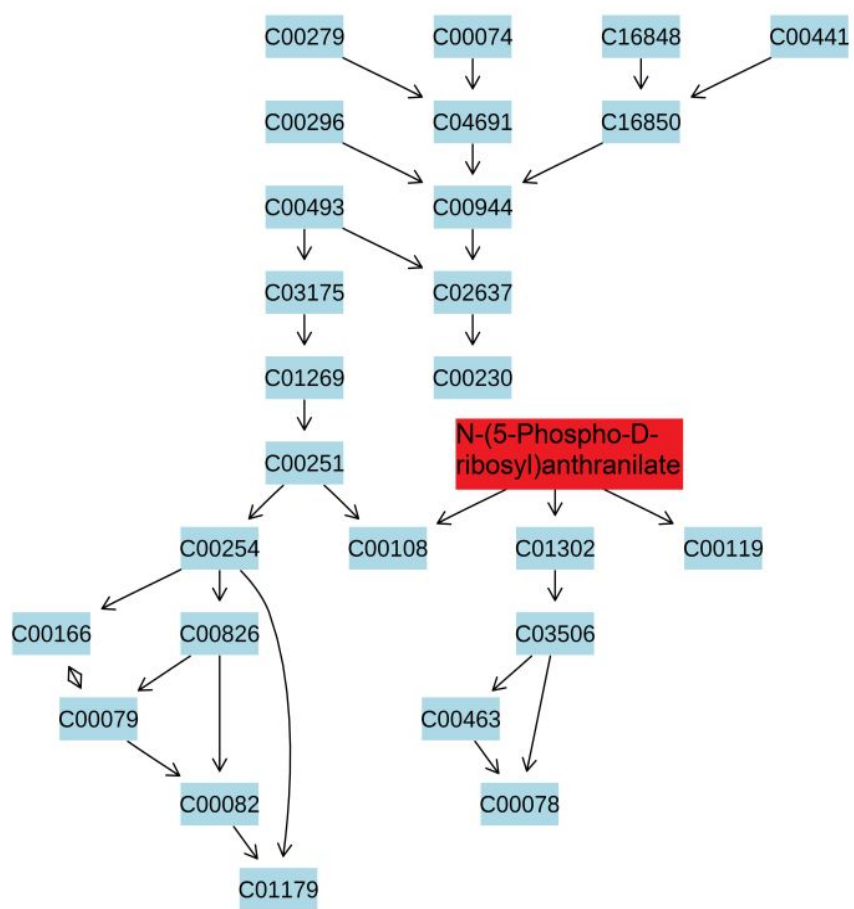


Table S1. Metabolomics Study on the Effect of (a) GTE, (b) EGCG, (c) M1, (d) M2, and (e) Bevacizumab Influencing on HUVEC Growth Induced by VEGF. Seven major groups of metabolites were expressed in the cells. Layer: Aq – extracted from aqueous layer and analyzed by hydrophobic chromatography; CH - extracted from chloroform layer and analyzed by hydrophilic chromatography. FC – fold change (response of different treatments/response of GTE treatment); <1 – downregulation, >1 – upregulation. * – p<0.05; ** – p<0.01; *** – p < 0.001.

(a)

	GTE effect on VEGF					
	Layer/ Ionization	Experimental ion mass (m/z)	Compound mass	Ionization species	Regulation (FC)	Molecular formula
Nucleotides metabolites						
Thymine***	CH/+	165.0097	126.0429	[M+K] ⁺	5.448	C ₅ H ₆ N ₂ O ₂
Ureidoglycine***	CH/+	116.0433	133.0487	[M+H-H ₂ O] ⁺	0.436	C ₃ H ₇ N ₃ O ₃
Adenine***	Aq/+	136.0594	135.0545	[M+H] ⁺	0.037	C ₅ H ₅ N ₅
Alloxan***	CH/+	143.0041	142.0015	[M+H] ⁺	3.084	C ₄ H ₂ N ₂ O ₄
FAPγ-adenine***	Aq/+	154.0706	153.0651	[M+H] ⁺	0.390	C ₅ H ₇ N ₅ O
8-OH,7-methylguanine***	Aq/+	182.0673	181.06	[M+H] ⁺	0.068	C ₆ H ₇ N ₅ O ₂
5-methyldeoxycytidine***	Aq/+	242.1104	241.1063	[M+H] ⁺	0.148	C ₁₀ H ₁₅ N ₃ O ₄
Uridine***	Aq/+	267.0608	244.0695	[M+Na] ⁺	0.025	C ₉ H ₁₂ N ₂ O ₆
adenosine***	Aq/+	268.1044	267.0968	[M+H] ⁺	0.331	C ₁₀ H ₁₃ N ₅ O ₄
2',3'-Cyclic UMP***	Aq/+	329.0129	306.0253	[M+Na] ⁺	2.454	C ₉ H ₁₁ N ₂ O ₈ P
kinetin-7-N-glucoside***	Aq/+	378.1461	377.1335	[M+H] ⁺	0.055	C ₁₆ H ₁₉ N ₅ O ₆
Uridine diphosphate (UDP) ***	CH/+	427.9931	404.0022	[M+Na] ⁺	1.969	C ₉ H ₁₄ N ₂ O ₁₂ P ₂
6-Mercaptopurine ribonucleoside 5'-diphosphate***	CH/+	408.9750	443.9906	[M+H-2H ₂ O] ⁺	2.183	C ₁₀ H ₁₄ N ₄ O ₁₀ P ₂ S
Deoxyuridine triphosphate (dUTP) ***	Aq/+	490.9600	467.9736	[M+Na] ⁺	2.311	C ₉ H ₁₅ N ₂ O ₁₄ P ₃
Uridine triphosphate (UTP) ***	Aq/+	484.9792	483.9685	[M+H] ⁺	11.182	C ₉ H ₁₅ N ₂ O ₁₅ P ₃
Uridine triphosphate (UTP) ***	CH/+	466.9662	483.9685	[M+H-H ₂ O] ⁺	16.786	C ₉ H ₁₅ N ₂ O ₁₅ P ₃
2'-Deoxyinosine triphosphate***	CH/+	493.916	491.9848	[M+H] ⁺	5.431	C ₁₀ H ₁₅ N ₄ O ₁₃ P ₃
Inosine triphosphate***	CH/+	509.9851	507.9798	[M+H] ⁺	1.996	C ₁₀ H ₁₅ N ₄ O ₁₄ P ₃
cADP-ribose***	Aq/+	542.0699	541.0611	[M+H] ⁺	0.012	C ₁₅ H ₂₁ N ₅ O ₁₃ P ₂

UDP-N-acetyl-D-galactosamine-4-sulphate***	Aq/+	710.0280	687.0384	[M+Na]+	0.001	C ₁₇ H ₂₇ N ₃ O ₂₀ P ₂ S
Amino acid metabolites and derivatives						
3-Mercaptolactate*	Aq/+	104.9962	122.0038	[M+H-H ₂ O]+	1.565	C ₃ H ₆ O ₃ S
L-leucine***	Aq/+	132.0960	131.0946	[M+H]+	0.241	C ₆ H ₁₃ NO ₂
L-phenylalanine***	Aq/+	166.0871	165.079	[M+H]+	0.266	C ₉ H ₁₁ NO ₂
L-3-phenylacetic acid***	Aq/+	189.0507	166.063	[M+Na]+	0.213	C ₉ H ₁₀ O ₃
L-3-Phenyllacetic acid***	Aq/+	167.0760	166.063	[M+H]+	0.253	C ₉ H ₁₀ O ₃
L-tyrosine***	Aq/+	182.0773	181.0739	[M+H]+	0.068	C ₉ H ₁₁ NO ₃
L-homocysteic acid***	Aq/+	184.0233	183.0201	[M+H]+	0.545	C ₄ H ₉ NO ₅ S
2,4-dihydroxy-2-heptenediic acid***	Aq/+	191.0515	190.0477	[M+H]+	0.441	C ₇ H ₁₀ O ₆
Xanthurenic acid***	Aq/+	206.0479	205.0375	[M+H]+	0.228	C ₁₀ H ₇ NO ₄
N-Acetyl-L-phenylalanine***	Aq/+	190.0887	207.0895	[M+H-H ₂ O]+	0.032	C ₁₁ H ₁₃ NO ₃
L-prolyl-L-proline***	Aq/+	213.1240	212.1161	[M+H]+	0.027	C ₁₀ H ₁₆ N ₂ O ₃
Prolyl-Threonine***	CH/+	217.1113	216.111	[M+H]+	7.735	C ₉ H ₁₆ N ₂ O ₄
L-Ornithino-L-alanine***	Aq/+	220.1278	219.1219	[M+H]+	0.033	C ₈ H ₁₇ N ₃ O ₄
Cystathionine***	CH/+	223.0736	222.0674	[M+H]+	0.016	C ₇ H ₁₄ N ₂ O ₄ S
L-Cystine***	CH/+	263.0122	240.0238	[M+Na]+	1.787	C ₆ H ₁₂ N ₂ O ₄ S ₂
Asparaginyln-Leucine***	Aq/+	246.1444	245.1376	[M+H]+	0.331	C ₁₀ H ₁₉ N ₃ O ₄
Asparaginyln-Methionine***	Aq/+	264.1036	263.094	[M+H]+	0.124	C ₉ H ₁₇ N ₃ O ₄ S
S-Ribosyl-L-homocysteine***	Aq/+	268.0944	267.0777	[M+H]+	0.331	C ₉ H ₁₇ NO ₆ S
Gly-Thr-OH***	Aq/+	307.0868	284.0645	[M+Na]+	0.048	C ₆ H ₁₂ N ₂ O ₄
Asp-Ala-OH***	Aq/+	351.0237	312.0594	[M+K]+	0.695	C ₁₂ H ₁₂ N ₂ O ₈
Vitamins and coenzymes metabolites						
4-Pyridoxic acid***	CH/+	184.0619	183.0532	[M+H]+	2.221	C ₈ H ₉ NO ₄
Dexpanthenol***	Aq/+	170.1203	205.1314	[M+H-2H ₂ O]+	0.256	C ₉ H ₁₉ NO ₄
Dexpanthenol***	Aq/+	188.1339	205.1314	[M+H-H ₂ O]+	0.169	C ₉ H ₁₉ NO ₄
2-Amino-3-oxo-4-phosphonoxybutyrate***	Aq/+	214.0084	213.0038	[M+H]+	0.275	C ₄ H ₈ NO ₇ P
2-Oxo-3-hydroxy-4-phosphobutanoate***	Aq/+	196.9831	213.9879	[M+H-H ₂ O]+	72.194	C ₄ H ₇ O ₈ P
Pantothenic Acid***	Aq/+	220.1178	219.1107	[M+H]+	0.033	C ₉ H ₁₇ NO ₅

tetrahydro-L-Biopterin***	Aq/+	264.1036	241.1175	[M+Na]+	0.124	C ₉ H ₁₅ N ₅ O ₃
Gamma-Glutamyl-Se-methylselenocysteine***	Aq/+	350.9871	312.0224	[M+K]+	1.594	C ₉ H ₁₆ N ₂ O ₅ Se
6-(3'-Triphosphoryl-1'-methylglyceryl)-7-methyl-7,8-dihydrobiopterin***	Aq/+	524.0355	523.027	[M+H]+	0.005	C ₁₁ H ₂₀ N ₅ O ₁₃ P ₃
Nicotinamide adenine dinucleotide (NAD)***	Aq/+	664.1139	663.1091	[M+H]+	0.019	C ₂₁ H ₂₇ N ₇ O ₁₄ P ₂
Antioxidant metabolites						
Magnesium L-ascorbic acid-2-phosphate***	Aq/+	260.9664	277.9678	[M+H-H ₂ O]+	7.735	C ₆ H ₇ MgO ₉ P
Membrane lipid metabolites						
2,5-Octadien-1-ol***	CH/+	109.0989	126.1045	[M+H-H ₂ O]+	8.716	C ₈ H ₁₄ O
γ-heptenoic acid***	Aq/+	167.0996	128.0837	[M+H]+	0.259	C ₇ H ₁₂ O ₂
6E,8E-decadienoic acid***	CH/+	169.1289	168.115	[M+H]+	> 1000	C ₁₀ H ₁₆ O ₂
4-n-valeryl butyric acid***	CH/+	195.1128	172.1099	[M+Na]+	0.032	C ₉ H ₁₆ O ₃
10-Hydroxy-2,8-decadiene-4,6-dienoic acid***	Aq/+	177.0572	176.0473	[M+H]+	0.419	C ₁₀ H ₈ O ₃
9-oxo-2E-decenoic acid***	Aq/+	185.1131	184.1099	[M+H]+	0.039	C ₁₀ H ₁₆ O ₃
Decenedioic acid***	CH/+	223.0971	200.1049	[M+Na]+	0.074	C ₁₀ H ₁₆ O ₄
DHAP(8:0) ***	CH/+	297.1118	296.1025	[M+H]+	0.100	C ₁₁ H ₂₁ O ₇ P
PC(2:0/2:0***)	Aq/+	364.1127	341.124	[M+Na]+	0.040	C ₁₂ H ₂₄ NO ₈ P
Cer(d16:2(4E,6E)/22:1(13Z)(2OH)) ***	Aq/+	606.5427	605.5383	[M+H]+	1.298	C ₃₈ H ₇₁ NO ₄
Ceramide (d18:1/22:0) ***	Aq/+	604.6032	621.606	[M+H-H ₂ O]+	1.289	C ₄₀ H ₇₉ NO ₃
GlcCer(d18:1/12:0) ***	Aq/+	664.4744	641.4867	[M+Na]+	1.457	C ₃₆ H ₆₇ NO ₈
PC(O-16:0/12:0) ***	Aq/+	664.5241	663.5203	[M+H]+	1.515	C ₃₆ H ₇₄ NO ₇ P
GlcCer(d15:2(4E,6E)/18:0) ***	Aq/+	666.5344	683.5336	[M+H-H ₂ O]+	1.457	C ₃₉ H ₇₃ NO ₈
PS(22:4(7Z,10Z,13Z,16Z)/14:1(9Z)) ***	Aq/+	782.4962	781.4894	[M+H]+	1.281	C ₄₂ H ₇₂ NO ₁₀ P
Sugar metabolites						
Succinic acid***	CH/+	101.0208	118.0266	[M+H-H ₂ O]+	0.036	C ₄ H ₆ O ₄
Formyl phosphate***	Aq/+	164.9358	125.9718	[M+K]+	0.144	CH ₃ O ₅ P
(S)-2-Hydroxyglutarate***	CH/+	149.0476	148.0372	[M+H]+	>1000	C ₅ H ₈ O ₅
D-Ribonolactone***	Aq/+	186.9994	148.0372	[M+K]+	0.706	C ₅ H ₈ O ₅

Ribonic acid***	CH/+	167.0603	166.0477	[M+H] ⁺	0.268	C ₅ H ₁₀ O ₆
D-Glycerate 2-phosphate***	Aq/+	186.9993	185.9929	[M+H] ⁺	1.842	C ₃ H ₇ O ₇ P
D-4-O-Methyl-myo-inositol*	Aq/+	217.0733	194.079	[M+Na] ⁺	0.153	C ₇ H ₁₄ O ₆
Carboxyphosphonopyruvate***	CH/+	196.9869	195.9773	[M+H] ⁺	>1000	C ₄ H ₅ O ₇ P
Oxalomalic Acid*	CH/+	244.966	206.0063	[M+K] ⁺	1.663	C ₆ H ₆ O ₈
Oxalomalic Acid*	Aq/+	244.9704	206.0063	[M+K] ⁺	3.865	C ₆ H ₆ O ₈
Ribose 1-phosphate***	Aq/+	268.987	230.0192	[M+K] ⁺	0.755	C ₅ H ₁₁ O ₈ P
5'-Oxoinosine***	Aq/+	267.0698	266.0651	[M+H] ⁺	0.025	C ₁₀ H ₁₀ N ₄ O ₅
Inosine triphosphate***	Aq/+	508.9851	507.9798	[M+H] ⁺	1.996	C ₁₀ H ₁₅ N ₄ O ₁₄ P ₃
UDP-L-Ara4FN***	Aq/+	564.0598	563.0554	[M+H] ⁺	0.026	C ₁₅ H ₂₃ N ₃ O ₁₆ P ₂
Phenolic acids metabolites						
cis-4-Carboxymethylenebut-2-en-4-olide***	Aq/+	104.9990	140.011	[M+H-2H ₂ O] ⁺	2.010	C ₆ H ₄ O ₄
L-threo-3-Methylmalate*	Aq/+	186.9989	148.0372	[M+K] ⁺	3.636	C ₅ H ₈ O ₅
4-Sulfobenzaldehyde*	Aq/+	185.9987	186.9949	[M+H] ⁺	3.636	C ₇ H ₅ O ₄ S ⁻
3-Sulfomuconate**	Aq/+	244.9720	221.9834	[M+Na] ⁺	2.130	C ₆ H ₆ O ₇ S
4-Sulfolactone***	Aq/+	244.9714	221.9834	[M+Na] ⁺	3.865	C ₆ H ₆ O ₇ S
Vanillin 4-sulfate***	Aq/+	254.9939	232.0041	[M+Na] ⁺	1.732	C ₈ H ₈ O ₆ S
Dihydrocaffeic acid 3-sulfate***	CH/+	284.9996	262.0147	[M+Na] ⁺	2.253	C ₉ H ₁₀ O ₇ S
Caftaric acid***	Aq/+	351.0111	312.0481	[M+K] ⁺	1.594	C ₁₃ H ₁₂ O ₉
Digallate***	CH/+	345.0240	322.0325	[M+Na] ⁺	1.872	C ₁₄ H ₁₀ O ₉
Quercetin 3,7-dimethyl ether 4'-sulfate***	Aq/+	433.0204	410.0308	[M+Na] ⁺	1.563	C ₁₇ H ₁₄ O ₁₀ S
Axillarin 7-sulfate***	CH/+	427.0331	426.0257	[M+H] ⁺	31.235	C ₁₇ H ₁₄ O ₁₁ S
Quercetin 3,7-di-O-sulfate***	CH/+	484.9492	461.9563	[M+Na] ⁺	14.871	C ₁₅ H ₁₀ O ₁₃ S ₂
Epitheafagallin 3-O-gallate***	CH/+	591.0584	552.0904	[M+K] ⁺	2.379	C ₂₇ H ₂₀ O ₁₃

(b)

	EGCG effect on VEGF					
	Layer/ Ionization	Experimental ion mass (m/z)	Compound mass	Ionization species	Regulation (FC)	Molecular formula
Nucleotides metabolites						
Cytosine***	Aq/+	112.0512	111.0433	[M+H] ⁺	4.365	C ₄ H ₅ N ₃ O
L-Dihydroorotic acid**	Aq/+	159.0414	158.0328	[M+H] ⁺	4.753	C ₅ H ₆ N ₂ O ₄
Adenosine*	Aq/+	268.1045	267.0968	[M+H] ⁺	0.813	C ₁₀ H ₁₃ N ₅ O ₄
5'-Deoxy-5'-(methylthio)adenosine***	Aq/+	298.0978	297.0896	[M+H] ⁺	3.190	C ₁₁ H ₁₅ N ₅ O ₃ S
Cyclic CMP***	Aq/+	306.0500	305.0413	[M+H] ⁺	3.986	C ₉ H ₁₂ N ₃ O ₇ P
Cytidine 2'-phosphate***	Aq/+	324.0639	323.0519	[M+H] ⁺	20.443	C ₉ H ₁₂ N ₃ O ₈ P ²⁻
2',3'-Cyclic GMP***	Aq/+	346.0543	345.0474	[M+H] ⁺	3.865	C ₁₀ H ₁₂ N ₅ O ₇ P
2',3'-Cyclic GMP***	Aq/+;CH/+	328.0471	345.0474	[M+H-H ₂ O] ⁺	20.217	C ₁₀ H ₁₂ N ₅ O ₇ P
ADP***	Aq/+	428.0377	427.0294	[M+H] ⁺	1.781	C ₁₀ H ₁₅ N ₅ O ₁₀ P ₂
Amino acid metabolites and derivatives						
Putrescine***	Aq/+	127.0607	88.1	[M+K] ⁺	1.614	C ₄ H ₁₂ N ₂
5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone*	Aq/-	141.0524	142.063	[M-H] ⁻	0.000	C ₇ H ₁₀ O ₃
L-Leucine***	Aq/+	132.0998	131.0946	[M+H] ⁺	1.345	C ₆ H ₁₃ NO ₂
D-erythro-3-Methylmalate**	Aq/+	149.0414	148.0372	[M+H] ⁺	0.586	C ₅ H ₈ O ₅
L-Methionine***	Aq/+	150.0545	149.051	[M+H] ⁺	2.055	C ₃ H ₁₁ NO ₂ S
4-Hydroxycyclohexylacetic acid***	Aq/+	181.0877	158.0943	[M+Na] ⁺	4.449	C ₈ H ₁₄ O ₃
D-Ala-D-Ala*	Aq/+	141.0624	160.0848	[M-H ₂ O-H] ⁻	0.000	C ₆ H ₁₂ N ₂ O ₃
L-Tyrosine**	Aq/+	182.0785	181.0739	[M+H] ⁺	1.368	C ₉ H ₁₁ NO ₃
Hydroxyphenyllactic acid***	Aq/+	183.0614	182.0579	[M+H] ⁺	2.129	C ₉ H ₁₀ O ₄
Carboxyspermidine***	Aq/+	172.1486	189.1477	[M+H-H ₂ O] ⁺	2.598	C ₈ H ₁₉ N ₃ O ₂
Threoninyl-Proline***	Aq/+	217.1028	216.111	[M+H] ⁺	1.874	C ₉ H ₁₆ N ₂ O ₄
Hydroxypropyl-L-Valine*	Aq/+	213.1183	230.1267	[M+H-H ₂ O] ⁺	0.013	C ₁₀ H ₁₈ N ₂ O ₄
Lysyl-Serine***	Aq/+	256.1273	233.1376	[M+Na] ⁺	2.725	C ₉ H ₁₉ N ₃ O ₄
Ser-Trp-OH***	Aq/+	436.1125	413.1223	[M+Na] ⁺	3.718	C ₂₀ H ₁₉ N ₃ O ₇

Vitamins and coenzymes metabolites						
Pyridoxine (Vitamin B6) ***	Aq/+	170.0794	169.0739	[M+H] ⁺	4.501	C ₈ H ₁₁ NO ₃
4-Pyridoxic acid***	Aq/+	206.0402	183.0532	[M+Na] ⁺	0.540	C ₈ H ₉ NO ₄
2-Amino-3-oxo-4-phosphonooxybutyrate***	Aq/+	214.0099	213.0038	[M+H] ⁺	0.303	C ₄ H ₈ NO ₇ P
5-Amino-6-(5'-phosphoribosylamino)uracil***	Aq/+	355.0701	354.0577	[M+H] ⁺	4.393	C ₉ H ₁₅ N ₄ O ₉ P
Nicotinamide adenine dinucleotide (NAD) ***	Aq/+	664.1177	663.1091	[M+H] ⁺	2.011	C ₂₁ H ₂₇ N ₇ O ₁₄ P ₂
Antioxidant metabolites						
Phosphoroselenoic acid***	Aq/+	200.8512	161.8985	[M+K] ⁺	0.650	H ₃ O ₃ PSe
Methylselenopyruvate***	Aq/+	220.9012	181.9482	[M+K] ⁺	0.505	C ₄ H ₆ O ₃ Se
S-(Hydroxymethyl)glutathione***	Aq/+	320.0945	337.0944	[M+H-H ₂ O] ⁺	1.800	C ₁₁ H ₁₉ N ₃ O ₇ S
(R)-S-Lactoylglutathione***	Aq/+	380.1123	379.1049	[M+H] ⁺	4.328	C ₁₃ H ₂₁ N ₃ O ₈ S
3-Phosphoglycerol-glutathione***	Aq/+	484.0731	461.0869	[M+Na] ⁺	1.594	C ₁₃ H ₂₄ N ₃ O ₁₁ PS
Glutathione, oxidized***	Aq/+;CH/+	613.1588	612.152	[M+H] ⁺	7.772	C ₂₀ H ₃₂ N ₆ O ₁₂ S ₂
Glutathione, oxidized***	Aq/+	635.1411	612.152	[M+Na] ⁺	2.441	C ₂₀ H ₃₂ N ₆ O ₁₂ S ₂
Membrane lipid metabolites						
2-Oxo-4-methylthiobutanoic acid***	Aq/+	149.0274	148.0194	[M+H] ⁺	0.507	C ₅ H ₈ O ₃ S
2-Furoylglycine***	Aq/+	170.0396	169.0375	[M+H] ⁺	0.066	C ₇ H ₇ NO ₄
Phosphodimethylethanolamine***	Aq/+	192.0436	169.0504	[M+Na] ⁺	0.281	C ₄ H ₁₂ NO ₄ P
2-hydroxy capric acid***	Aq/+;CH/+	211.1298	188.1412	[M+Na] ⁺	4.202	C ₁₀ H ₂₀ O ₃
2,6-Dimethyl-1,8-octanedioic acid*	Aq/+;CH/+	203.1217	202.1205	[M+H] ⁺	2.666	C ₁₀ H ₁₈ O ₄
12-amino-dodecanoic acid***	Aq/-	236.1620	215.1885	[M+Na-2H] ⁻	70.260	C ₁₂ H ₂₅ NO ₂
14-Pentadecynoic acid***	Aq/+	277.1586	238.1933	[M+K] ⁺	3.366	C ₁₅ H ₂₆ O ₂
Cer(d18:0/h17:0) ***	Aq/+;CH/+	608.5079	569.5383	[M+K] ⁺	0.453	C ₃₅ H ₇₁ NO ₄
Cer(d16:1(4E)/20:0(2OH)) ***	Aq/+;CH+	604.5293	581.5383	[M+Na] ⁺	0.530	C ₃₆ H ₇₁ NO ₄
Cer(d18:0/18:0(2OH)) ***	Aq/+;CH+	606.5497	583.554	[M+Na] ⁺	0.499	C ₃₆ H ₇₃ NO ₄
Cer(d16:1/23:0) ***	Aq/+	630.5861	607.5903	[M+Na] ⁺	0.577	C ₃₉ H ₇₇ NO ₃
Cer(d16:1(4E)/22:0(2OH)) ***	Aq/+	632.6009	609.5696	[M+Na] ⁺	0.582	C ₃₈ H ₇₅ NO ₄
Cer(t20:0/20:0(2OH)) ***	Aq/+	678.6036	655.6115	[M+Na] ⁺	0.328	C ₄₀ H ₈₁ NO ₅

Sugar metabolites						
Ethylene glycol***	Aq/+	101.0022	62.0368	[M+K]+	7.681	C ₂ H ₆ O ₂
Formyl phosphate**	Aq/+	164.9366	125.9718	[M+K]+	0.650	CH ₃ O ₅ P
D-Galactosamine*	Aq/+	180.0886	179.0794	[M+H]+	0.066	C ₆ H ₁₃ NO ₅
2-Hydroxy-dATP**	Aq/+	508.0079	506.9957	[M+H]+	2.778	C ₁₀ H ₁₆ N ₅ O ₁₃ P ₃
Phenolic acids metabolites						
Phenol***	Aq/+	117.0334	94.0419	[M+Na]+	0.612	C ₆ H ₆ O
Methyl benzoate***	Aq/+	137.0599	136.0524	[M+H]+	1.528	C ₈ H ₈ O ₂
2,6-Dimethoxyphenol***	Aq/+	155.0668	154.063	[M+H]+	2.821	C ₈ H ₁₀ O ₃
Ferulic acid***	Aq/+	195.0593	194.0579	[M+H]+	6.399	C ₁₀ H ₁₀ O ₄
Epigallocatechin***	Aq/+	307.0839	306.074	[M+H]+	3.812	C ₁₅ H ₁₄ O ₇
4-Methoxybenzyl O-(2-sulfoglucoside) ***	Aq/+	381.0823	380.0777	[M+H]+	3.226	C ₁₄ H ₂₀ O ₁₀ S

(c)

	M1 effect on VEGF					
	Layer/ Ionization	Experimental ion mass (m/z)	Compound mass	Ionization species	Regulation (FC)	Molecular formula
Nucleotides metabolites						
7-Methylinosine***	CH/+	265.0992	282.0964	[M+H-H ₂ O] ⁺	0.422	C ₁₁ H ₁₅ N ₄ O ₅
7-Methylinosine**	CH/+	283.1058	283.1042	[M] ⁺	0.553	C ₁₁ H ₁₅ N ₄ O ₅ ⁺
2-Aminoadenosine**	CH/+	283.1123	282.1077	[M+H] ⁺	0.487	C ₁₀ H ₁₄ N ₆ O ₄
Amino acid metabolites and derivatives						
3-Mercaptolactate***	CH/+	104.9984	122.0038	[M+H-H ₂ O] ⁺	9.602	C ₃ H ₆ O ₃ S
L-(-)-3-Phenyllactic acid**	Aq/+	205.0204	166.063	[M+K] ⁺	0.152	C ₉ H ₁₀ O ₃
Phosphohydroxypyruvic acid**	CH/+	222.9447	183.9773	[M+K] ⁺	5.581	C ₃ H ₅ O ₇ P
4-Sulfolactone***	CH/+	244.9742	221.9834	[M+Na] ⁺	12.632	C ₆ H ₆ O ₃ S
4a-Hydroxytetrahydrobiopterin**	CH/+	280.1010	257.1124	[M+Na] ⁺	1.748	C ₉ H ₁₅ N ₅ O ₄
Antioxidant metabolites						
Methylselenopyruvate**	CH/+	182.9525	181.9482	[M+H] ⁺	0.098	C ₄ H ₆ O ₃ Se
Vitamins and coenzymes metabolites						
Pantothenic Acid**	Aq/+	220.1201	219.1107	[M+H] ⁺	0.110	C ₉ H ₁₇ NO ₅
Reduced riboflavin**	CH/+	401.1442	378.1539	[M+Na] ⁺	0.539	C ₁₇ H ₂₂ N ₄ O ₆
Membrane lipid metabolites						
N-(3-oxo-hexanoyl)-homoserine lactone***	CH/+	214.1060	213.1001	[M+H] ⁺	0.259	C ₁₀ H ₁₅ NO ₄
N-heptanoyl-homoserine lactone*	Aq/+	214.1441	213.1365	[M+H] ⁺	4.246	C ₁₁ H ₁₉ NO ₃
Undecanedioic acid*	CH/+	217.1385	216.1362	[M+H] ⁺	2.000	C ₁₁ H ₂₀ O ₄

9-Decenoylcholine*	CH/+	274.2644	256.2277	[M+NH4] ⁺	0.380	C ₁₅ H ₃₀ NO ₂ ⁺
4-hydroxy palmitic acid*	Aq/+	290.2620	272.2351	[M+NH4] ⁺	0.559	C ₁₆ H ₃₂ O ₃
Cer(d18:2/21:0) ***	Aq/+	606.5857	605.5747	[M+H] ⁺	0.240	C ₃₉ H ₇₅ NO ₃
Sugar metabolites						
PPP _i *	CH/+	222.8937	257.9096	[M+H-2H ₂ O] ⁺	0.545	H ₅ O ₁₀ P ₃
PPP _i	Aq/+	222.9146	257.9096	[M+H-2H ₂ O] ⁺	0.651	H ₅ O ₁₀ P ₃
PPP _i ***	Aq/+	280.8946	257.9096	[M+Na] ⁺	0.645	H ₅ O ₁₀ P ₃
Phenolic acids metabolites						
Phloroglucinol**	CH/+	149.0207	126.0317	[M+Na] ⁺	0.484	C ₆ H ₆ O ₃
4-Sulfo benzaldehyde***	Aq/+	187.0082	185.9987	[M+2H] ⁺	13.527	C ₇ H ₅ O ₄ S ⁻
4-Sulfo benzoate***	Aq/+	240.9595	201.9936	[M+K] ⁺	1.839	C ₇ H ₆ O ₅ S
2-allyl-5-methyldecahydroquinolin-6-ol*	Aq/+	192.1733	209.178	[M+H-H ₂ O] ⁺	4.467	C ₁₃ H ₂₃ NO
Vanillin 4-sulfate***	Aq/+	254.9939	232.0041	[M+Na] ⁺	22.254	C ₈ H ₈ O ₆ S
Apigenin 7-sulfate***	Aq/+	351.0202	350.0096	[M+H] ⁺	21.501	C ₁₅ H ₁₀ O ₈ S

(d)

	M2 effect on VEGF					
	Layer/ Ionization	Experimental ion mass (m/z)	Compound mass	Ionization species	Regulation (FC)	Molecular formula
Nucleotides metabolites						
Adenosine*	Aq/+	268.1026	267.0968	[M+H] ⁺	0.512	C ₁₀ H ₁₃ N ₅ O ₄
Xanthosine 5'-pyrophosphate (XDP)***	Aq/+	408.9991	444.0084	[M+H-2H ₂ O] ⁺	37.372	C ₁₀ H ₁₄ N ₄ O ₁₂ P ₂
Amino acid metabolites and derivatives						
3-Mercaptolactate***	Aq/+	104.9984	122.0038	[M+H-H ₂ O] ⁺	13.700	C ₃ H ₆ O ₃ S
L-(-)-3-Phenyllactic acid*	CH/+	205.0264	166.063	[M+K] ⁺	0.288	C ₉ H ₁₀ O ₃
Guanidinosuccinic Acid*	Aq/+	176.0714	175.0593	[M+H] ⁺	7.714	C ₅ H ₉ N ₃ O ₄
meso-2,6-Diaminoheptanedioate*	CH/+	213.0873	190.0954	[M+Na] ⁺	0.050	C ₇ H ₁₄ N ₂ O ₄
Gamma-glutamyl-Isoleucine*	Aq/+	242.1491	259.1532	[M+H-H ₂ O] ⁺	>1000	C ₁₁ H ₂₁ N ₃ O ₄
Arginyl-Asparagine*	CH/+	272.1324	289.1386	[M+H-H ₂ O] ⁺	0.556	C ₁₀ H ₁₉ N ₅ O ₅
Asp-Ser-OH***	Aq/+	351.0442	328.0543	[M+Na] ⁺	48.146	C ₁₂ H ₁₂ N ₂ O ₉
Antioxidant metabolites						
Phosphoroselenoic acid***	Aq/+	200.8795	161.8985	[M+K] ⁺	0.415	H ₃ O ₃ PSe
Methylselenopyruvate***	Aq/+	164.9468	181.9482	[M+H-H ₂ O] ⁺	0.465	C ₄ H ₆ O ₃ Se
Methylselenopyruvate*	CH/+	182.9525	181.9482	[M+H] ⁺	0.209	C ₄ H ₆ O ₃ Se
Vitamins and coenzymes metabolites						
Pantothenic Acid*	Aq/+	220.1201	219.1107	[M+H] ⁺	0.049	C ₉ H ₁₇ NO ₅
Membrane lipid metabolites						
11E-Tetradecen-1-ol*	CH/+	230.2497	212.214	[M+NH ₄] ⁺	0.204	C ₁₄ H ₂₈ O
2-Hydroxymyristic Acid***	CH/+	262.2381	244.2038	[M+NH ₄] ⁺	0.380	C ₁₄ H ₂₈ O ₃
5-Nonyltetrahydro-2-oxo-3-furancarboxylic acid*	CH/+	274.2086	256.1675	[M+NH ₄] ⁺	3.088	C ₁₄ H ₂₄ O ₄
9-Decenoylcholine***	CH/+	274.2644	256.2277	[M+NH ₄] ⁺	0.241	C ₁₅ H ₃₀ NO ₂
MG(0:0/14:0/0:0) ***	CH/+	325.2381	302.2457	[M+Na] ⁺	2.525	C ₁₇ H ₃₄ O ₄

Sugar metabolites						
Phosphohydroxypyruvic acid**	Aq/+	222.9447	183.9773	[M+K] ⁺	5.421	C ₃ H ₅ O ₇ P
PPPi***	Aq/+	222.8946	257.9096	[M+H-2H ₂ O] ⁺	0.359	H ₅ O ₁₀ P ₃
PPPi***	Aq/+	280.8946	257.9096	[M+Na] ⁺	0.351	H ₅ O ₁₀ P ₃
Phenolic acids metabolites						
4-Sulfobenzaldehyde***	Aq/+	187.0082	185.9987	[M+2H] ⁺	19.327	C ₇ H ₅ O ₄ S ⁻
Flaviolin***	Aq/+	244.9842	206.0215	[M+K] ⁺	13.639	C ₁₀ H ₆ O ₅
Vanillin 4-sulfate***	Aq/+	254.9939	232.0041	[M+Na] ⁺	35.27	C ₈ H ₈ O ₆ S
Rhamnazin 3-O-sulfate***	Aq/+	433.0226	410.0308	[M+Na] ⁺	117.072	C ₁₇ H ₁₄ O ₁₀ S
6-Hydroxyluteolin 6,3'-dimethyl ether 7,4'-disulfate***	Aq/+	491.0002	489.9876	[M+H] ⁺	78.571	C ₁₇ H ₁₄ O ₁₃ S ₂

(e)

	Avastin effect on VEGF					
	Layer/ Ionization	Experimental ion mass (m/z)	Compound mass	Ionization species	Regulation (FC)	Molecular formula
Nucleotides metabolites						
Amino acid metabolites and derivatives						
Trimethylammonioacetate**	Aq/+	140.0697	117.0790	[M+Na] ⁺	<0.01	C ₅ H ₁₁ NO ₂
4-(2-Furanylmethylene)-3,4-dihydro-2H-pyrrole*	CH/+	170.0582	147.0684	[M+Na] ⁺	<0.01	C ₉ H ₉ NO
4-Acetylimidazo[4,5-c]pyridine*	CH/+	184.0488	161.0589	[M+Na] ⁺	2.017	C ₈ H ₇ N ₃ O
Alanyl-Arginine*	Aq/+	268.1304	245.1488	[M+Na] ⁺	0.336	C ₉ H ₁₉ N ₅ O ₃
Dopamine glucuronide**	Aq/+	330.1139	329.1111	[M+H] ⁺	0.378	C ₁₄ H ₁₉ NO ₈
N-(5-Phospho-D-ribosyl)anthranilate*	Aq/+	314.0398	349.0563	[M+H-2H ₂ O] ⁺	<0.01	C ₁₂ H ₁₆ NO ₉ P
Vitamins and coenzymes metabolites						
Pyridoxine (Vitamin B6) ***	CH/+	192.0637	169.0739	[M+Na] ⁺	0.814	C ₈ H ₁₁ NO ₃
Membrane lipid metabolites						
DG(17:2(9Z,12Z)/17:2(9Z,12Z)/0:0) ***	Aq/+;CH/+	589.4819	588.4754	[M+H] ⁺	> 1000	C ₃₇ H ₆₄ O ₅
DG(14:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0) *	Aq/+;CH/+	611.4680	610.4597	[M+H] ⁺	555.650	C ₃₉ H ₆₂ O ₅
DG(17:2(9Z,12Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)[iso2] **	Aq/+;CH/+	633.4899	650.491	[M+H-H ₂ O] ⁺	387.910	C ₄₂ H ₆₆ O ₅
DG(17:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)[iso2] **	Aq/+;CH/+	655.5295	654.5223	[M+H] ⁺	> 1000	C ₄₂ H ₇₀ O ₅
PE-Cer(d14:2(4E,6E)/20:1(11Z)(2OH)) **	Aq/+;CH/+	655.4862	672.4842	[M+H-H ₂ O] ⁺	129.120	C ₃₆ H ₆₉ N ₂ O ₇ P
Cer(d18:1/26:1(17Z)) **	Aq/+;CH/+	714.6178	675.6529	[M+K] ⁺	0.374	C ₄₄ H ₈₅ NO ₃
PA(14:1(9Z)/22:4(7Z,10Z,13Z,16Z)) *	Aq/+;CH/+	677.4544	694.4574	[M+H-H ₂ O] ⁺	304.204	C ₃₉ H ₆₇ O ₈ P
PG(12:0/20:3(8Z,11Z,14Z)) *	Aq/+;CH/+	699.4688	716.4628	[M+H-H ₂ O] ⁺	210.806	C ₃₈ H ₆₉ O ₁₀ P

N-Glycolylganglioside GM2**	Aq/+;CH/+	744.6327	743.6275	[M+H] ⁺	5.490	C ₄₃ H ₈₅ NO ₈
PS(17:2(9Z,12Z)/22:4(7Z,10Z,13Z,16Z)) *	Aq/+;CH/+	844.5151	821.5207	[M+Na] ⁺	6.216	C ₄₅ H ₇₆ NO ₁₀ P
PS(17:0/22:4(7Z,10Z,13Z,16Z)) *	Aq/+;CH/+	826.5537	825.552	[M+H] ⁺	> 1000	C ₄₅ H ₈₀ NO ₁₀ P
PS(17:0/22:2(13Z,16Z)) *	Aq/+;CH/+	830.5967	829.5833	[M+H] ⁺	2.639	C ₄₅ H ₈₄ NO ₁₀ P
PS(20:0/22:4(7Z,10Z,13Z,16Z)) ***	Aq/+;CH/+	866.6608	865.6561	[M+H] ⁺	13.495	C ₅₀ H ₉₂ NO ₈ P