

SUPPORTING INFORMATION(SI):

Large-Scale Target Identification of Herbal Medicine Using a Reverse Docking Approach

Haiping Zhang^{1,2 †}, Jianbo Pan^{3 †}, Xuli Wu⁴, Ai-Ren Zuo⁵, Yanjie Wei^{2}, Zhi-Liang Ji^{1*}*

¹State Key Laboratory of Stress Cell Biology, School of Life Sciences, Xiamen University, Xiamen, Fujian, 361102, PR China

²Joint Engineering Research Center for Health Big Data Intelligent Analysis Technology, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong Province, People's Republic of China, 518055

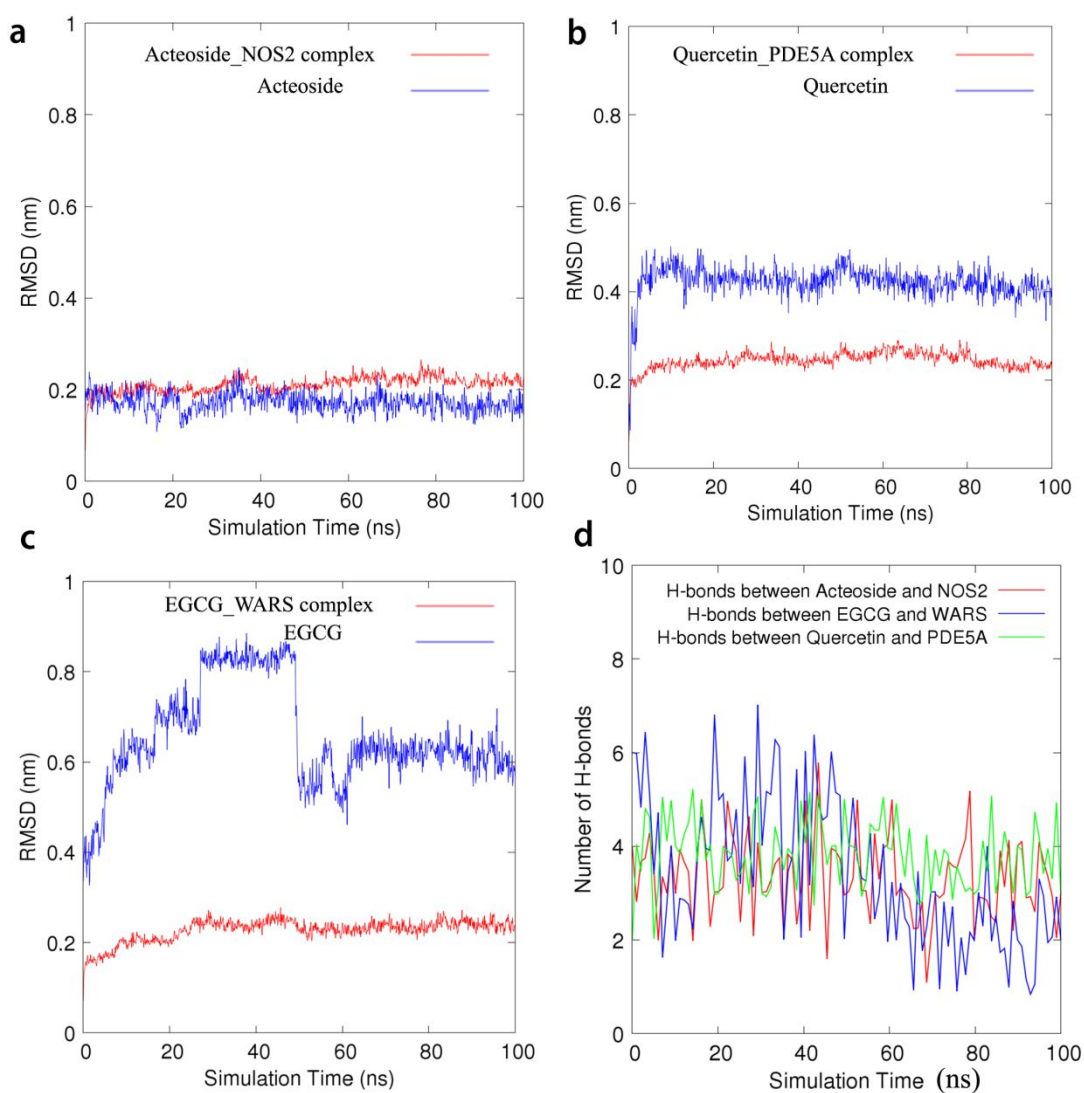
³Department of Ophthalmology, Johns Hopkins School of Medicine, Baltimore, MD, USA, 21205

⁴School of Medicine, Shenzhen University, Shenzhen, Guangdong Province, People's Republic of China, 518060

⁵Jiangxi University of Traditional Chinese Medicine, Nanchang, Jiangxi, China

[†]These authors have contributed equally as first authors.

*Corresponding author: Zhi-Liang Ji: appo@xmu.edu.cn, Yanjie Wei: yj.wei@siat.ac.cn



Supplementary Figure S1. Post simulation analyses by the MD simulation. With the initial structures as reference structures, the RMSD values of the simulation trajectories are shown in Panel a, b, c for of acteoside_NOS2 (PDBID 4nos), quercetin_PDE5A (PDBID 2h44), and EGCG_WARS (PDBID 1r6t) complexes respectively. For the hydrogen bond numbers, only the hydrogen bonds between ligand and protein were counted. Panel c indicates that binding style of WARS (PDBID 1r6t) and EGCG has changes during the first 60 ns simulation, while become relative stable late. Panel d shows the number of hydrogen bonds formed between ligand and protein.

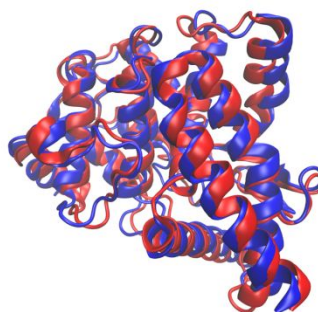
a Replicates of
Acteoside_NOS2 complex

RMSD: 0.224 nm



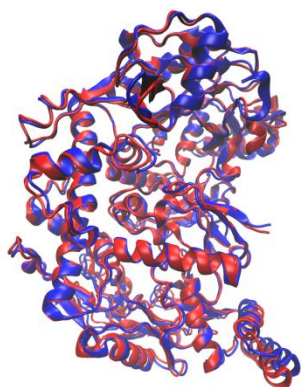
b Replicates of
Quercetin_PDE5A complex

RMSD: 0.265 nm

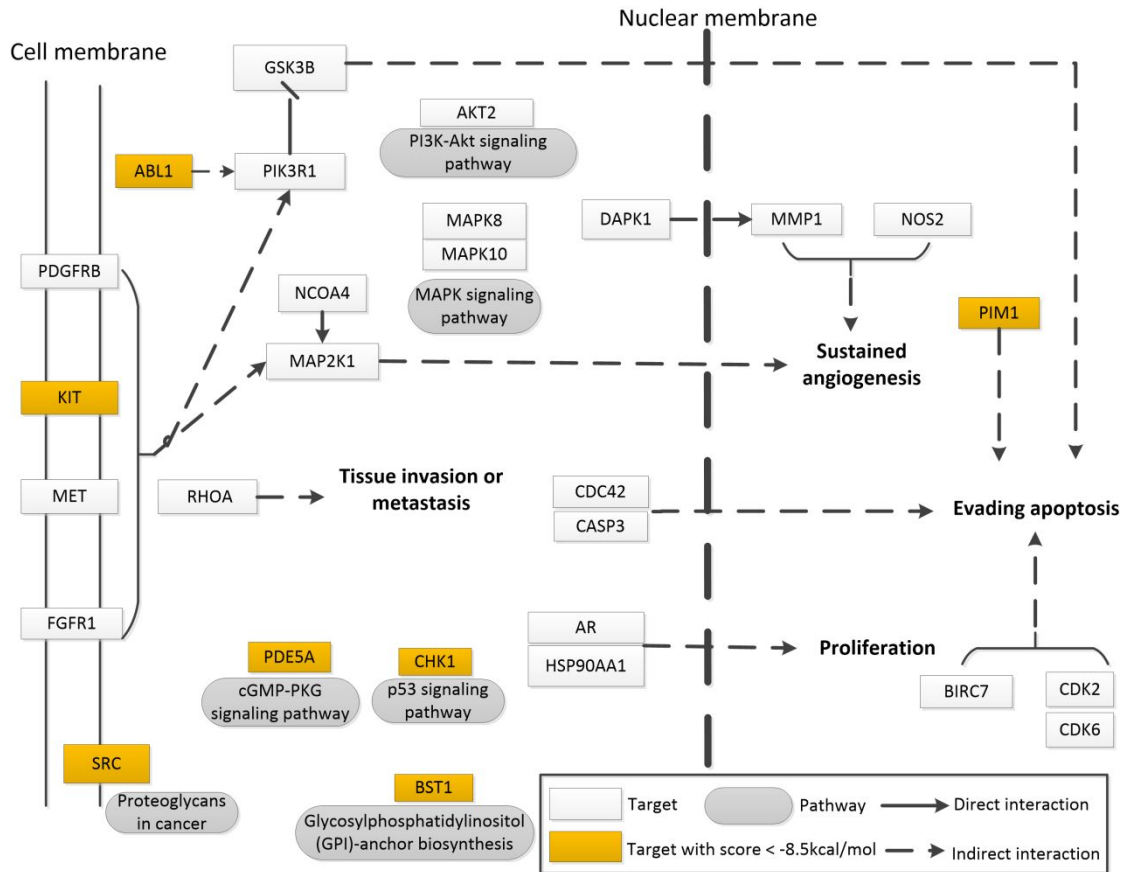


c Replicates of
EGCG_WARS complex

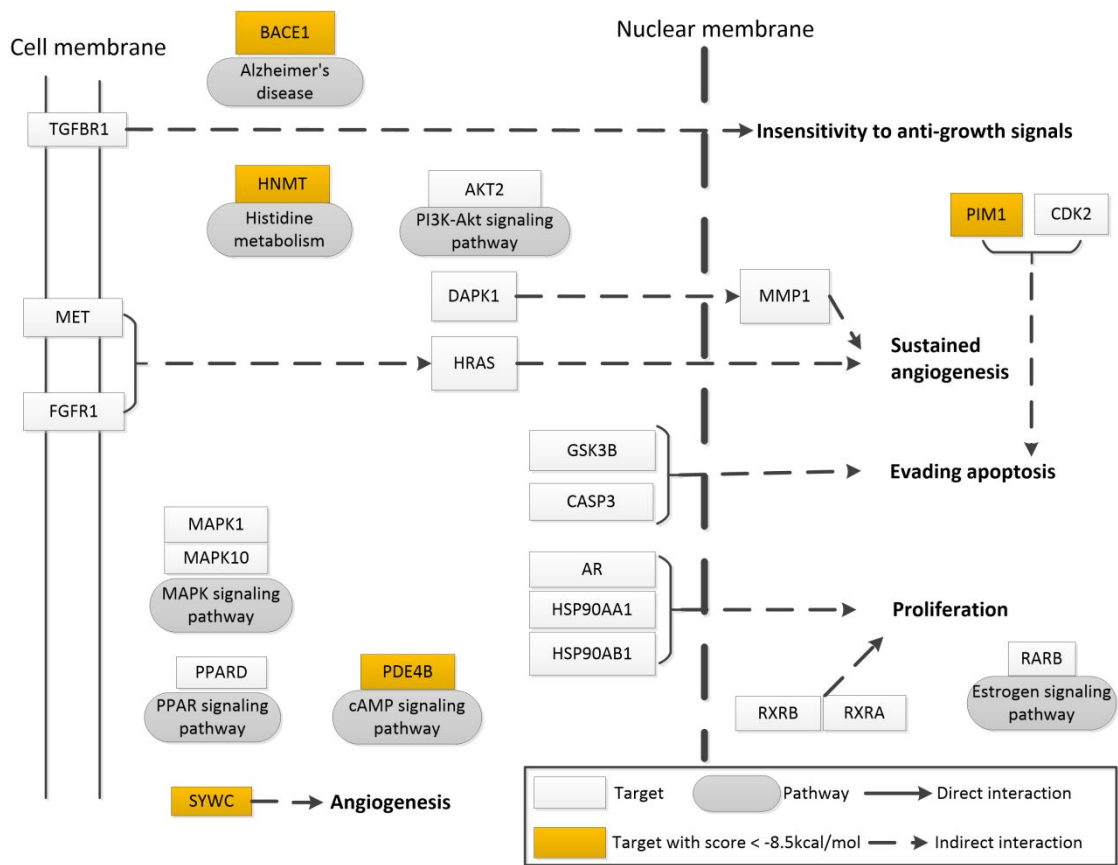
RMSD: 0.266 nm



Supplementary Figure S2. Overlap protein conformation snapshot from two independent MD simulations. In order to ensure the robust of the MD simulation, we carry post simulation analyses for the other MD simulation which have the same simulation condition except a random initial velocity. With the initial structures as reference structures, the last frame conformations from the simulation trajectories are superposed. It was shown in Panel a, b, c for of acteoside_NOS2 (PDBID 4nos), quercetin_PDE5A (PDBID 2h44), and EGCG_WARS (PDBID 1r6t) complexes respectively. The proteins in these 3 cases are pretty stable during the simulation, with RMSD value of 0.224nm, 0.265nm, 0.266nm for the superposed last frame protein conformations. It shows highly consistent with the Supplementary Figure S1, indicating the reliability of the MD simulation for these three systems.



Supplementary Figure S3. A pharmacology network of quercetin was constructed by mapping the potential targets to KEGG pathway.



Supplementary Figure S4. A pharmacology network of EGCG was constructed by mapping the potential targets to the KEGG pathways.

Table S1. The list of highly potential targets of acetoside predicted by the pipeline. The gene names with bold font are known target according to reports.

Name	Indications	PDB ID	Vina score	Vina score#	Full name of known ligand	Ingredient target relation
			(Kcal/mol)	(comparative known ligand in PDB) (Kcal/mol)		
Nitric oxide synthase, inducible(NOS2)	Asthma; Mucositis; Migraine; Neuropathic pain; Inflammation; Chronic obstructive pulmonary disease; etc	4nos	-10.3	-10.1(HEM)	PROTOPORPHYRIN IX CONTAINING FE	Inhibitor ¹⁻² ; Influence the activity of nitric oxide synthase ³ .
		1nsi	-9.5	-10.6(HEM)	PROTOPORPHYRIN IX CONTAINING FE	
cAMP-specific 3,5-cyclic phosphodiesterase 4B (PDE4)	Chronic obstructive pulmonary disease; Asthma	1ror	-10.3	-3.7(AMP)	ADENOSINE MONOPHOSPHATE	Inhibition activity against cAMP phosphodiesterase of Acetoside' analogs plantamajoside ⁴⁻⁵
		1ro9	-10.1	-5.3(8BR)	8-BROMO-ADENOSINE-5'-MONOPHOSPHATE	

Corticosteroid 11-beta-dehydrogenase isozyme 1	Non-insulin dependent diabetes; Rheumatoid arthritis; Diabetes mellitus; Obesity; etc	2bel	-9.9	-6.6(NAP)	NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE	Unknown
Glutathione reductase, mitochondrial(GSR)	Nutritional supplementation	1dnc	-9.8	-9.2(FAD)	FLAVIN-ADENINE DINUCLEOTIDE	Neuroprotective activity ⁶
ADP-ribosyl cyclase 2	Hematological neoplasm; Multiple myeloma	1isj	-9.7	-4.1(NMN)	BETA-NICOTINAMIDE RIBOSE MONOPHOSPHATE	Unknown
		1isg	-9.4	-3.9(AGS)	PHOSPHOTHIOPHOSPHORIC ACID-ADENYLATE ESTER	
		1ish	-9	-1.6(ENP)	ETHENO-NADP	
Inosine-5-monophosphate dehydrogenase 2 (IMPDH2)	Autoimmune disease; Transplant rejection; cancer	1b3o	-9.5	-2.6(SAE)	SELENAZOLE-4-CARBOXYAMIDE-ADENINE DINUCLEOTIDE	Unknown
Leukotriene A-4 hydrolase	Inflammation; Cancer; etc	1gw6	-9.4	-4.6(BES)	2-(3-AMINO-2-HYDROXY-4-PHENYL-BUTYRYLAMINO)-4-METHYL-PENTANOIC ACID	Unknown
Proto-oncogene serine/threonine-protein kinase Pim-1	Cancer	2bik	-9.4	-9.2(BI1)	3-{1-[3-(DIMETHYLAMINO)PROPYL]-1H-INDOL-3-YL}-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE	Unknown

Beta-secretase 1	Alzheimers disease	2g94	-9.4	-5.8(ZPQ)	N~2~-[(2R,4S,5S)-5-{{N-{{(3,5-DIMETHYL-1H-PYRAZOL-1-YL)METHOXY}CARBONYL}-3-(METHYLSULFONYL)-L-ALANYL}AMINO}-4-HYDROXY-2,7-DIMETHYLOCTANOYL]-N-ISOBUTYL-L-VALINAMIDE	Unknown
		1m4h	-9.3	-3.0(1OL)	(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoic acid	
Renin	Glaucoma; Renal disease; Hypertension; etc	1bim	-9.3	-7.1(0QB)	(2S)-2-[(2-amino-1,3-thiazol-4-yl)methyl]-N~1~-{(1S,2S)-1-(cyclohexylmethyl)-2-hydroxy-2-[(3R)-1,5,5-trimethyl-2-oxopyrrolidin-3-yl]ethyl}-N~4~-[2-(dimethylamino)-2-oxoethyl]-N~4~-[(1S)-1-phenylethyl]butanediamide	Unknown
Cathepsin K	Multiple sclerosis; Asthma; Cancer; Autoimmune disease; etc	1tu6	-9.3	0.2(FSP)	[1-(4-FLUOROBENZYL)CYCLOBUTYL]METHYL (1S)-1-[OXO(1H-PYRAZOL-5-YLAMINO)ACETYL]PENTYL CARBAMATE	Unknown
Macrophage metalloelastase	Chronic obstructive pulmonary disease	1utz	-9.3	-8.2(PF3)	(2R)-3-({[4-[(PYRIDIN-4-YL)PHENYL]-THIEN-2-YL}CARBOXAMIDO)(PHENYL)PROPANOIC ACID	Unknown
Phenylalanine-4-hydroxylase	Phenylketonuria; Hypertension; etc	1dmw	-9.1	-5.0(HBI)	7,8-DIHYDROBIOPTERIN	Unknown
Hydroxyacyl-coenzyme A dehydrogenase, mitochondrial	Parkinsons disease, chronic fatigue syndrome,	1f12	-9.1	-3.4(3HC)	3-HYDROXYBUTANOYL-COENZYME A	Unknown

	Alzheimers disease and cardiovascular disease.	1f0y	-8.8	-3.4(CAA)	ACETOACETYL-COENZYME A	
Proto-oncogene tyrosine-protein kinase Src	Hypercalcemia; Cancer; Osteoporosis; Cerebrovascular ischemia; Bone metastases; Metastasis; Solid tumor	2bdj	-9.1	-7.5(HET)	3-[2-(2-CYCLOPENTYL-6-{[4-(DIMETHYLPHOSPHORYL)PHENYL]AMINO}-9H-PURIN-9-YL)ETHYL]PHENOL	Unknown
Ornithine aminotransferase, mitochondrial	Cancer	2can	-9.1	-4.8(PLP)	PYRIDOXAL-5'-PHOSPHATE	Unknown
Prothrombin	Deep vein thrombosis; Wound healing; etc	1ad8	-9	-2.3(MDL)	[DEHYDROXY-N-METHYL-TYROSYL-PROLINYL]-[4,4,5,5,5-PENTAFLUORO-3-OXY-1-[3-INDOLYL]-PENT-2-YL]AMINE	Unknown
		1bmn	-9	-0.3(BM9)	[S-(R*,R*)]-1-(AMINOIMINOMETHYL)-N-[[1-[N-(2-NAPHTHALENYLSULFONYL)-L-SERYL]-3-PYRROLIDINYL]METHYL]-3-PIPERIDENECARBOXAMIDE	
Aldose reductase (AKR1B1)	Neuropathy; Central nervous system disease; Diabetic	1az1	-9	-8.1(NAP)	NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE	Strong inhibitor ⁷⁻⁸

Ras-related protein Rab-9A	Psoriasis;Cancer; Rheumatoid arthritis;Cardiac failure;Inflammation;etc	1wms	-8.9	-4.5(GDP)	GUANOSINE-5'-DIPHOSPHATE	Unknown
Carbonic anhydrase 2	Parkinsons disease; chronic fatigue syndrome; Alzheimers disease;etc.	1bnw	-8.8	-4.1(TPD)	N-(2-THIENYLMETHYL)-2,5-THIOPHENEDISULFONAMIDE	Unknown
Glycogen synthase kinase-3 beta	Central nervous system disease;Inflammation;etc	1j1c	-8.8	-4.7(ADP)	ADENOSINE-5'-DIPHOSPHATE	Unknown
		1j1b	-8.7	-4.6(ANP)	PHOSPHOAMINOPHOSPHONIC ACID-ADENYLATE ESTER	
Heat shock protein HSP 90-alpha	Alzheimers disease;Renal disease;Lipid metabolism disorder;etc	1uyk	-8.8	0.8(PUX)	8-BENZO[1,3]DIOXOL-,5-YLMETHYL-9-BUTYL-2-FLUORO-9H-PURIN-6-YLAMINE	Unknown
Thymidylate kinase	Alzheimers disease;Non-insulin dependent diabetes;Inflammation;Prostate tumor;Cancer;etc	1e9d	-8.7	-4.9(ATM)	3'-AZIDO-3'-DEOXYTHYMIDINE-5'-MONOPHOSPHATE	Unknown

Phosphoenolpyruvate carboxykinase, cytosolic	Ariboflavinosis	1khh	-8.7	-5.6(GCP)	PHOSPHOMETHYLPHOSPHONIC ACID GUANYLATE ESTER	Unknown
Cyclin-dependent kinase 2	Ariboflavinosis	1oi9*	-8.7	none		Unknown
		1dm2	-8.5	-7.8(HMD)	4-(5-AMINO-4-OXO-4H-PYRAZOL-3-YL)-2-BROMO-4,5,6,7-TETRAHYDRO-3AH-PYRROLO[2,3-C]AZEPIN-8-ONE	
Cyclin-A2	T-cell lymphoma;Autoimmune disease;Inflammation;etc	1oi9*	-8.7	none		Unknown
Purine nucleoside phosphorylase	Bacillus anthracis infection	1rfg	-8.7	-0.9(SO4)	SULFATE ION	Unknown
Carbonic anhydrase 2	Parkinsons disease; chronic fatigue syndrome; Alzheimers disease; etc	1i9p	-8.6	-4.2(IOE)	4-(AMINOSULFONYL)-N-[(2,4,6-TRIFLUOROPHENYL)METHYL]-BENZAMIDE	Unknown
Death-associated protein kinase 1	Psoriasis;Cancer; Rheumatoid arthritis;etc	1ig1	-8.6	-2.3(ANP)	PHOSPHOAMINOPHOSPHONIC ACID-ADENYLATE ESTER	Unknown

Ras-related botulinum substrate 1	C3 toxin	Toxicity;Metabolic disorder;Cancer; etc	1ryf	-8.5	-4.0(GDP)	GUANOSINE-5'-DIPHOSPHATE	Unknown
Pancreatic alpha-amylase		Alzheimers disease	1xcw	-8.5	-4.0(3SA)	ACARBOSE DERIVED TRISACCHARIDE	Unknown
Dual specificity protein kinase CLK1		Thromboembolism	1z57	-8.5	-7.4(DBQ)	DEBROMOHYMENIALDISINE	Unknown
# vina score determined for known ligand-protein complex downloaded from the PDB database							
* the PDB structure contains two protein units.							

Table S2. The list of highly potential targets of quercetin predicted by the pipeline. The gene names with bold font are known target according to reports.

Name	Indication	PDB id	Vina score	Vina score#	Full name of known ligand	Ingredient target relation
			(Kcal/mol)	(comparative known ligand in PDB) (Kcal/mol)		
cGMP-specific 3,5-cyclic phosphodiesterase (PDE5A)	Anal fissure; Raynauds disease; Cardiac failure; Thrombosis; Vascular disease; Cancer; etc	2h44	-10.2	-12.0(7CA)	5,7-DIHYDROXY-2-(4-METHOXYPHENYL)-8-(3-METHYLBUTYL)-4-OXO-4H-CHROMEN-3-YL 6-DEOXY-ALPHA-L-MANNOPYRANOSIDE	Inhibitor ⁹
Mast/stem cell growth factor receptor(SGFR or KIT)	Pancreas tumor; Ovary tumor; Cancer; Mastocytosis; Gastrointestinal tumor	1pkg	-10.1	-0.9(ADP) ‡	ADENOSINE-5'-DIPHOSPHATE	Inhibitor of EGFR (structure similar to SGFR) ¹⁰
Serine/threonine-protein kinase (Chk1)	Cancer; Solid tumor	2e9v	-9.6	-8.0(85A)	18-CHLORO-2-OXO-17-[(PYRIDIN-4-YLMETHYL)AMINO]-2,3,11,12,13,14-HEXAHYDRO-1H,10H-4,8-(AZENO)-9,15,1,3,6-BENZODIOXATRIAZACYCLOHEPTADECINE-7-CARBONITRILE	Inhibitor ¹¹
		2e9u	-8.9	-9.3(A25)	18-CHLORO-11,12,13,14-TETRAHYDRO-1H,10H-8,4-(AZENO)-9,15,1,3,6-BENZODIOXATRIAZACYCLOHEPTADECIN-2-ONE	

ADP-ribosyl cyclase 2	Hematological neoplasm; Multiple myeloma	1ish	-9.3	-1.6(ENP) ‡	ETHENO-NADP	Inhibit ADP-ribosyl-cyclase activity ¹²
		1isj	-8.6	-4.1(E22)	BETA-NICOTINAMIDE RIBOSE MONOPHOSPHATE	
Proto-oncogene tyrosine-protein kinase Src(SRC)	Hypercalcemia; Cancer; etc	2bdj	-9.3	-7.5(HET)	3-[2-(2-CYCLOPENTYL-6- {[4-(DIMETHYLPHOSPHORYL)PHE NYL]AMINO}-9H-PURIN-9-YL)ETHYL]PHENOL	Inhibitor ¹³
cAMP-specific 3,5-cyclic phosphodiesterase 4B(PDE4B)	Chronic obstructive pulmonary disease; Asthma	1ror	-9.1	-3.7(AMP) ‡	ADENOSINE MONOPHOSPHATE	Inhibitor ¹⁴
		1ro9	-9	-5.3(8BR)	8-BROMO-ADENOSINE-5'-MONOPHOSPHATE	
		1y2j	-8.8	none		
Proto-oncogene tyrosine-protein kinase LCK	Psoriasis; Cancer; Autoimmune disease; etc	1qpd	-9	-8.8(STU)	STAUROSPORINE	Unknown
		3bys	-8.9	-11.0(AM5)	4-methyl-N~3~-(2- {[4-(4-methylpiperazin-1-yl)phenyl]amino}pyrimidin-5-yl)-N~1~-[3-(trifluoromethyl)phenyl]benzene-1,3-dicarboxamide	

Tyrosine-prot ein kinase JAK2	Psoriasis; Cancer; Rheumatoid arthritis; Pulmonary hypertension; Myeloid leukemia;etc	2b7a	-9	-9.9(IZA)	2-TERT-BUTYL-9-FLUORO-3,6-DIHYDRO-7H-BENZ[H]-IMIDA Z[4,5-F]ISOQUINOLINE-7-ONE	Unknown
Glutathione S-transferase A1	Nutritional supplementatio n	1guh	-8.9	-5.0(GSB)	S-BENZYL-GLUTATHIONE	Unknown
Aldose reductase	Neuropathy; Diabetic neuropathy; Diabetic complication; Central nervous system disease; etc	2dux	-8.9	-6.8(NAP)	NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE	Unknown
Corticosteroi d 11-beta-dehy drogenase isozyme 1	Non-insulin dependent diabetes; Obesity; etc	2bel	-8.8	-6.6(NAP)	NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE	Unknown

Vascular endothelial growth factor receptor 2	Angiogenesis disorder; Melanoma; Cancer; etc	1y6b	-8.7	-7.9(AAX)	N-(CYCLOPROPYLMETHYL)-4-(METHYLOXY)-3-({5-[3-(3-PYRIDINYL)PHENYL]-1,3-OXAZOL-2-YL} AMINO)BENZENESULFONAMIDE	Unknown
Proto-oncogene tyrosine-protein kinase ABL1	Nutritional supplementation	2f4j	-8.7	-8.1(VX6)	CYCLOPROPANECARBOXYLIC ACID {4-[4-(4-METHYL-PIPERAZIN-1-YL)-6-(5-METHYL-2H-PYRAZOL-3-YLAMINO)-PYRIMIDIN-2-YLSULFANYL]-PHENYL}-AMIDE	Unknown
Estradiol 17-beta-dehydrogenase 1	Parkinsons disease, chronic fatigue syndrome, Alzheimers disease ; etc	1equ	-8.6	-6.7(EQI)	EQUILIN	Unknown
Thymidylate synthase	Small-cell lung cancer; Solid tumor; Cancer; etc	1i00	-8.6	-5.1(D16)	TOMUDEX	Unknown
Dual specificity mitogen-activated protein kinase kinase 1	Colon tumor; Melanoma; Cancer; etc	1s9j	-8.6	-4.9(ATP)	ADENOSINE-5'-TRIPHOSPHATE	Unknown

Adenosine kinase	Septic shock; Pain; Inflammation; Anesthesia; etc	1bx4	-8.5	-6.5(ADN)	ADENOSINE	Unknown
S-methyl-5-thioadenosine phosphorylase	Nutritional supplementation	1sd2	-8.5	-3.1(MTH) ‡	2-(4-AMINO-PYRROLO[2,3-D]PYRIMIDIN-7-YL)-5-METHYLSULFANYLMETHYL-TETRAHYDRO-FURAN-3,4-DIOL	Unknown
Proto-oncogene serine/threonine-protein kinase Pim-1	Cancer	1yxt	-8.5	0.5(ANP) ‡	PHOSPHOAMINOPHOSPHONIC ACID-ADENYLATE ESTER	inhibitor ¹⁵
Estrogen receptor beta(ESR2)	Osteoporosis in post-menopausal women	2qtu	-8.5	-7.0(3AS)	(3aS,4R,9bR)-2,2-difluoro-4-(4-hydroxyphenyl)-6-(methoxymethyl)-1,2,3,3a,4,9b-hexahydrocyclopenta[c]chromen-8-ol	Phytoestrogen-like activity ¹⁶

vina score determined for known ligand-protein complex downloaded from the PDB database.

‡ Some of the co-crystallized ligands have very low binding energy towards their targets, it indicates the score function of Vina may be failed in some cases. This often happens for the cases contain a chemical group that rarely happened in the training dataset of vina score.

Table S3. The list of highly potential targets of EGCG predicted by the pipeline. The gene names with bold front are known targets according to the reports.

Name	Indication	PDB ID	Vina score	Vina score#	Full name of known ligand	Ingredient target relation
			(Kcal/mol)	(comparative known ligand in PDB) (Kcal/mol)		
Tryptophanyl-tRNA synthetase, cytoplasmic (WARS)	Promoting healthy sleep, enhancing mental and emotional well-being, managing pain tolerance, and managing weight.	1r6t	-10.2	-8.4(TYM)	TRYPTOPHANYL-5'AMP	Downregulated by EGCG ¹⁷
Proto-oncogene serine/threonine-protein kinase Pim-1 (PIM1)	Cancer	2bik	-10.1	-9.2(BI1)	3-{1-[3-(DIMETHYLAMINO)PROPYL]-1H-INDOL-3-YL}-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE	Activity decreased by EGCG ¹⁸
		1xws	-10	-9.3(BI1)	3-{1-[3-(DIMETHYLAMINO)PROPYL]-1H-INDOL-3-YL}-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE	Up-regulated by EGCG ¹⁹
		1yxu	-9.8	-3.2(AMP)	ADENOSINE MONOPHOSPHATE	
Beta-secretase 1	Alzheimers disease	1m4h	-9.9	-3.0(1OL)	(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyl octanoic acid	Anti-β-secretase activity ²⁰
		2g94	-9.4	-5.8(ZPQ)		

cAMP-specific 3,5-cyclic phosphodiesterase 4B	Chronic obstructive pulmonary disease; Asthma	1ror	-9.8	-3.7(AMP)	ADENOSINE MONOPHOSPHATE	Unknown
Histamine N-methyltransferase	Acute malarial attacks in non-immune subjects.	1jqd	-9.2	-4.8(SAH)	S-ADENOSYL-L-HOMOCYSTEINE	Inhibitor of methyltransferase ²¹⁻²²
Estradiol 17-beta-dehydrogenase 1	Parkinsons disease, chronic fatigue syndrome, Alzheimers disease and cardiovascular disease.	1i5r	-9.1	-9.3(HYC)	O5'-[9-(3,17B-DIHYDROXY-1,3,5(10)-ESTRATRIEN-16B-YL)-NONANOYL]ADENOSINE	Unknown
		1equ	-8.8	-6.7(EQI)	EQUILIN	
Corticosteroid 11-beta-dehydrogenase isozyme 1	Non-insulin dependent diabetes; Rheumatoid arthritis; Diabetes mellitus; Obesity; etc	2bel	-9.1	-6.6(NAP)	NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE	Unknown
		3ch6	-8.5	-6.7(NAP)	NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE	
Leukotriene A-4 hydrolase	Inflammation; Cancer; etc	1gw6	-8.8	-4.6(BES)	2-(3-AMINO-2-HYDROXY-4-PHENYL-BUTYRYLAMINO)-4-METHYL-PENTANOIC ACID	Potential target ²³
Ornithine aminotransferase,	Cancer	2can	-8.8	-4.8(PLP)	PYRIDOXAL-5'-PHOSPHATE	Decreases expression ²⁴

mitochondrial						
Peroxisome proliferator-activated receptor alpha	Syndrome X; Lipid metabolism disorder; Congestive heart failure; Diabetes mellitus; Obesity; Inflammation; etc	1k7l	-8.7	-9.9(544)	2-(1-METHYL-3-OXO-3-PHENYL-PROPYLAMINO)-3-{4-[2-(5-METHYL-2-PHENYL-OXAZOL-4-YL)-ETHOXY]-PHENYL}-PROPIONIC ACID	Activation of PPAalpha ²⁵
Sorbitol dehydrogenase	Diabetic complication	1pl6	-8.7	-2.8(572)	4-[2-(HYDROXYMETHYL)PYRIMIDIN-4-YL]-N,N-DIMETHYLPIPERAZINE-1-SULFONAMIDE	Unknown
Proto-oncogene tyrosine-protein kinase LCK	Psoriasis; Cancer; Inflammation; Multiple sclerosis; Autoimmune disease; etc	1qpj	-8.7	-10.2(STU)	STAUROSPORINE	Unknown
Macrophage metalloelastase	Chronic obstructive pulmonary disease	1ros	-8.7	-7.8(DEO)	2-[2-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-YL)ETHYL]-4-(4'-ETHOXY-1,1'-BIPHENYL-4-YL)-4-OXOBUTANOIC ACID	Inhibitor ²⁶
ADP-ribosyl cyclase 2	Hematological neoplasm; Multiple myeloma	1ish	-8.6	-1.6(ENP)	ETHENO-NADP	Unknown
		1isj	-8.5	-4.1(NMN)	BETA-NICOTINAMIDE RIBOSE MONOPHOSPHATE	

Glutathione S-transferase A3	For nutritional supplementation, also for treating dietary shortage or imbalance	1tdi	-8.6	-2.9(GSH)	GLUTATHIONE	Enhance the detoxification of carcinogens ²⁷
Riboflavin kinase	For the treatment of ariboflavinosis (vitamin B2 deficiency).	1p4m	-8.5	-4.1(FMN)	FLAVIN MONONUCLEOTIDE	Unknown
Dipeptidyl peptidase 4	Rheumatoid arthritis; Diabetes mellitus; Non-insulin dependent diabetes; Autoimmune disease; Immune disorder	1u8e	-8.5	None		Unknown
Kinesin-like protein KIF11	Melanoma; Hodgkins disease; cancer	1yrs	-8.5	-5.3(ADP)	ADENOSINE-5'-DIPHOSPHATE	Unknown
Angiotensin-1 receptor	Retinopathy; Ovary tumor; Cancer	2p4i	-8.5	-11.1(MR9)	4-METHYL-3-({3-[2-(METHYLAMINO)PYRIMIDIN-4-YL]PYRIDIN-2-YL}OXY)-N-[2-MORPHOLIN-4-YL-5-(TRIFLUOROMETHYL)PHENYL]BENZAMIDE	Unknown
# vina score determined for known ligand-protein complex downloaded from the PDB database						

Table S4. Post simulation analyses for critical residues which involve in the binding interface of NOS2 (PDBID 4nos) with Acteoside, PDE5A (PDBID 2h44) with Quercetin, and WARS (PDBID 1r6t) with EGCG, respectively by g_mmpbsa program. Here only the residues that have free energy contribution larger than 3 kJ/mol or smaller than -3 kJ/mol were listed. The residue IDs are original IDs in the corresponding PDB without renumber.

Protein-ligand	Residue name and ID	Free energy contribution(kJ/mol)
NOS2-Acteoside (PDBID 4nos)	TRP-194	-9.63
	ARG-199	-4.9014
	CYS-200	-7.1893
	ILE-201	-9.3462
	ARG-203	-3.5962
	ARG-266	-3.8567
	PRO-350	-3.2311
	PHE-369	-5.6609
	TRP-372	-14.5526
	TYR-373	-5.3046
	MET-374	-9.5886
	GLU-377	21.5321
	ARG-381	-12.2301
	ASP-382	3.2481
	ASP-460	3.7834
	ILE-462	-8.8505
TRP-463	-4.5206	
WARS-EGCG (PDBID 1r6t)	ASP-312	9.9932
	GLN-313	-3.1124
	TYR-316	-3.0705
PDE5A-Quercetin	TYR-664	-4.3045

(PDBID 2h44)	ILE-665	-3.5423
	LEU-725	-3.2632
	ASP-764	-18.2668
	LEU-765	-5.6325
	LEU-804	-5.6604
	GLN-817	-11.1203
	PHE-820	-12.5587

Table S5. The KEGG pathway enrichment analysis for acetoside.

KEGG_PATHWAY	Count	%	pValue	Genes
hsa01100:Metabolic pathways	53	30.29	4.07E-07	GNPDA1, IMPA1, PNMT, HMGCR, DTYMK, HEXB, MAN1B1, LSS, PNP, ITPKA, GSTZ1, SPR, NOS2, HADH, AMY2A, IMPDH2, NMNAT3, ACADM, BST1, NME2, RFK, ADK, HSD11B1, OAT, NMNAT1, ALDOA, BCAT2, AHCY, SORD, HSD17B1, DCK, PAH, PPCDC, HPRT1, ACAT1, IVD, ATIC, ARG2, UCK2, PAPSS1, AMD1, HPGDS, UAP1, FDPS, PCK1, GPI, DHFR, GCK, PYGL, AKR1B1, LTA4H, ABO, DUT
hsa05200:Pathways in cancer	20	11.43	0.000798	EGFR, AR, HRAS, HSP90AA1, MMP9, MET, BIRC7, MAPK10, KIT, CDK2, DAPK1, TGFB2, AKT1, CASP3, RAC2, GSK3B, RAC1, PDGFRB, NOS2, PIK3R1
hsa04151:PI3K-Akt signaling pathway	18	10.29	0.001237	EGFR, HRAS, HSP90AA1, MET, KIT, CDK2, EPHA2, KDR, PCK1, AKT1, PDPK1, EIF4E, GSK3B, RAC1, PDGFRB, INSR, PIK3R1, IL2
hsa01130:Biosynthesis of antibiotics	17	9.71	1.26E-05	ALDOA, UAP1, ACADM, BCAT2, HMGCR, FDPS, LSS, ACAT1, PCK1, GPI, NME2, GCK, ATIC, ARG2, PAPSS1, HADH, OAT
hsa05205:Proteoglycans in cancer	16	9.14	2.58E-05	EGFR, HRAS, MMP9, MET, ESR1, PPP1CC, SRC, KDR, TGFB2, AKT1, PDPK1, CASP3, MAPK12, MAPK14, RAC1, PIK3R1
hsa04015:Rap1 signaling pathway	15	8.57	0.000173	EGFR, HRAS, MET, KIT, EPHA2, SRC, KDR, AKT1, RAC2, MAPK12, MAPK14, RAC1, PDGFRB, INSR, PIK3R1

hsa04014:Ras signaling pathway	15	8.5 7	0.00037	EGFR, HRAS, MET, KIT, MAPK10, EPHA2, KDR, AKT1, RAC2, RAC1, RAB5A, PDGFRB, INSR, RASA1, PIK3R1
hsa04510:Focal adhesion	14	8	0.000505	EGFR, AKT1, PDPK1, HRAS, RAC2, GSK3B, RAC1, MET, PDGFRB, MAPK10, PPP1CC, PIK3R1, SRC, KDR
hsa04910:Insulin signaling pathway	13	7.4 3	4.09E-05	HRAS, MAPK10, PPP1CC, PCK1, AKT1, PDPK1, EIF4E, GCK, PYGL, GSK3B, PTPN1, INSR, PIK3R1
hsa00230:Purine metabolism	13	7.4 3	0.000416	FHIT, NME2, GMPR2, ATIC, ADK, PDE4B, DCK, PDE4D, GMPR, PAPSS1, HPRT1, PNP, IMPDH2
hsa05152:Tuberculosis	13	7.4 3	0.000438	AKT1, VDR, CASP3, MAPK12, MAPK14, RAB5A, EEA1, APAF1, MAPK10, CTSS, NOS2, SRC, TGFB2
hsa04010:MAPK signaling pathway	13	7.4 3	0.009255	AKT1, EGFR, CASP3, HRAS, RAC2, MAPK12, MAPK14, RAC1, PDGFRB, HSPA1A, MAPK10, RASA1, TGFB2
hsa04068:FoxO signaling pathway	12	6.8 6	0.000145	AKT1, EGFR, PDPK1, HRAS, MAPK12, MAPK14, MAPK10, INSR, PIK3R1, CDK2, TGFB2, PCK1
hsa05145:Toxoplasmosis	11	6.2 9	0.000226	AKT1, PDPK1, CASP3, MAPK12, MAPK14, BIRC7, HSPA1A, MAPK10, NOS2, PIK3R1, TGFB2
hsa05161:Hepatitis B	11	6.2 9	0.001159	AKT1, CASP3, HRAS, MMP9, APAF1, MAPK10, CCNA2, PIK3R1, SRC, CDK2, TGFB2

hsa05203:Viral carcinogenesis	11	6.2	0.01348	CASP3, HRAS, KAT2B, RAC1, CHEK1, HIST1H4I, CCNA2, HDAC8, PIK3R1, SRC, CDK2
hsa05166:HTLV-I infection	11	6.2	0.05135	AKT1, HRAS, KAT2B, GSK3B, LCK, FDPS, PDGFRB, CHEK1, PIK3R1, TGFB2, IL2
hsa04664:Fc epsilon RI signaling pathway	10	5.7	1.39E-05	AKT1, PDPK1, HRAS, RAC2, MAPK12, MAPK14, RAC1, MAPK10, PIK3R1, BTK
hsa04917:Prolactin signaling pathway	10	5.7	1.99E-05	AKT1, HRAS, MAPK12, GSK, MAPK14, GSK3B, ESR1, MAPK10, PIK3R1, SRC
hsa05215:Prostate cancer	10	5.7	0.000112	AKT1, EGFR, AR, PDPK1, HRAS, HSP90AA1, GSK3B, PDGFRB, PIK3R1, CDK2
hsa04931:Insulin resistance	10	5.7	0.000528	AKT1, PDPK1, PYGL, GSK3B, PTPN1, MAPK10, PPP1CC, INSR, PIK3R1, PCK1
hsa04919:Thyroid hormone signaling pathway	10	5.7	0.000784	AKT1, PDPK1, HRAS, KAT2B, THRA, THRB, GSK3B, ESR1, PIK3R1, SRC
hsa04722:Neurotrophin signaling pathway	10	5.7	0.001133	AKT1, PDPK1, HRAS, MAPK12, MAPK14, GSK3B, RAC1, MAPK10, PIK3R1, ARHGDI1
hsa04380:Osteoclast differentiation	10	5.7	0.002094	AKT1, CTSK, MAPK12, MAPK14, LCK, RAC1, MAPK10, PIK3R1, TGFB2, BTK
hsa04144:Endocytosis	10	5.7	0.107949	EGFR, HRAS, MET, RAB5A, EEA1, HSPA1A, KIT, SRC, KDR, TGFB2
hsa04370:VEGF signaling pathway	9	5.1	4.55E-05	AKT1, HRAS, RAC2, MAPK12, MAPK14, RAC1, PIK3R1, SRC, KDR

hsa00980:Metabolism of xenobiotics by cytochrome P450	9	5.1	0.000183	GSTM1, GSTA1, GSTM2, AKR1C2, GSTA3, GSTT2B, SULT2A1, HSD11B1, GSTP1
hsa05204:Chemical carcinogenesis	9	5.1	0.000316	GSTM1, GSTA1, GSTM2, GSTA3, GSTT2B, SULT2A1, SULT1A1, HSD11B1, GSTP1
hsa04915:Estrogen signaling pathway	9	5.1	0.00132	AKT1, EGFR, HRAS, HSP90AA1, MMP9, ESR1, HSPA1A, PIK3R1, SRC
hsa05231:Choline metabolism in cancer	9	5.1	0.001502	AKT1, EGFR, PDPK1, HRAS, RAC2, RAC1, PDGFRB, MAPK10, PIK3R1
hsa04660:T cell receptor signaling pathway	9	5.1	0.001704	AKT1, PDPK1, HRAS, MAPK12, MAPK14, GSK3B, LCK, PIK3R1, IL2
hsa04668:TNF signaling pathway	9	5.1	0.002047	AKT1, CASP3, MAPK12, MAPK14, MMP9, MAPK10, MMP3, SELE, PIK3R1
hsa04071:Sphingolipid signaling pathway	9	5.1	0.004423	AKT1, PDPK1, HRAS, RAC2, MAPK12, MAPK14, RAC1, MAPK10, PIK3R1
hsa04611:Platelet activation	9	5.1	0.007133	AKT1, FGG, MAPK12, MAPK14, GP1BA, PPP1CC, PIK3R1, SRC, BTK
hsa05160:Hepatitis C	9	5.1	0.00815	AKT1, EGFR, PDPK1, HRAS, MAPK12, MAPK14, GSK3B, MAPK10, PIK3R1
hsa05164:Influenza A	9	5.1	0.035221	AKT1, MAPK12, MAPK14, GSK3B, DDX39B, FDPS, HSPA1A, MAPK10, PIK3R1
hsa05169:Epstein-Barr virus infection	9	5.1	0.054269	AKT1, MAPK12, MAPK14, GSK3B, HSPA1A, MAPK10, CCNA2, PIK3R1, CDK2

hsa04810:Regulation of actin cytoskeleton	9	5.1	0.087829	EGFR, HRAS, RAC2, F2, RAC1, PDGFRB, PPP1CC, PIK3R1, SRC
hsa05210:Colorectal cancer	8	4.5	0.000357	AKT1, CASP3, RAC2, GSK3B, RAC1, MAPK10, PIK3R1, TGFB2
hsa05230:Central carbon metabolism in cancer	8	4.5	0.000435	AKT1, EGFR, HRAS, GSK3B, MET, PDGFRB, KIT, PIK3R1
hsa05120:Epithelial cell signaling in Helicobacter pylori infection	8	4.5	0.000577	EGFR, CASP3, MAPK12, MAPK14, RAC1, MET, MAPK10, SRC
hsa04914:Progesterone-mediated oocyte maturation	8	4.5	0.002704	AKT1, HSP90AA1, MAPK12, MAPK14, MAPK10, CCNA2, PIK3R1, CDK2
hsa05142:Chagas disease (American trypanosomiasis)	8	4.5	0.007246	AKT1, MAPK12, MAPK14, MAPK10, NOS2, PIK3R1, TGFB2, IL2
hsa04152:AMPK signaling pathway	8	4.5	0.016572	AKT1, PDPK1, HMGCR, PFKFB1, CCNA2, INSR, PIK3R1, PCK1
hsa04024:cAMP signaling pathway	8	4.5	0.138751	AKT1, RAC2, PDE4B, RAC1, PDE4D, MAPK10, PPP1CC, PIK3R1
hsa05206:MicroRNAs in cancer	8	4.5	0.424525	EGFR, CASP3, HRAS, MMP9, MET, PIM1, PDGFRB, TGFB2
hsa00480:Glutathione metabolism	7	4	0.000762	GSTM1, GSTA1, GSTM2, GSR, GSTA3, GSTT2B, GSTP1
hsa05212:Pancreatic cancer	7	4	0.002724	AKT1, EGFR, RAC2, RAC1, MAPK10, PIK3R1, TGFB2

hsa04662:B cell receptor signaling pathway	7	4	0.003683	AKT1, HRAS, RAC2, GSK3B, RAC1, PIK3R1, BTK
hsa04610:Complement and coagulation cascades	7	4	0.003683	F11, FGG, F10, F3, F2, SERPINA1, F7
hsa04520:Adherens junction	7	4	0.004247	EGFR, RAC2, RAC1, MET, PTPN1, INSR, SRC
hsa05222:Small cell lung cancer	7	4	0.010133	AKT1, FHIT, BIRC7, APAF1, NOS2, PIK3R1, CDK2
hsa04012:ErbB signaling pathway	7	4	0.011295	AKT1, EGFR, HRAS, GSK3B, MAPK10, PIK3R1, SRC
hsa04620:Toll-like receptor signaling pathway	7	4	0.027362	AKT1, CTSK, MAPK12, MAPK14, RAC1, MAPK10, PIK3R1
hsa04360:Axon guidance	7	4	0.057603	HRAS, RAC2, GSK3B, RAC1, MET, RASA1, EPHA2
hsa05162:Measles	7	4	0.068899	AKT1, RAB9A, GSK3B, HSPA1A, PIK3R1, CDK2, IL2
hsa04932:Non-alcoholic fatty liver disease (NAFLD)	7	4	0.109928	AKT1, CASP3, GSK3B, RAC1, MAPK10, INSR, PIK3R1
hsa04062:Chemokine signaling pathway	7	4	0.216943	AKT1, HRAS, RAC2, GSK3B, RAC1, PIK3R1, SRC
hsa04060:Cytokine-cytokine receptor interaction	7	4	0.382645	EGFR, MET, PDGFRB, KIT, KDR, TGFB2, IL2

hsa00520:Amino sugar and nucleotide sugar metabolism	6	3.4	0.003641	GPI, UAP1, GNPDA1, GCK, HEXB, CHIT1
		3		
hsa05014:Amyotrophic lateral sclerosis (ALS)	6	3.4	0.004352	CASP3, MAPK12, MAPK14, RAC1, RAB5A, APAF1
		3		
hsa05213:Endometrial cancer	6	3.4	0.005157	AKT1, EGFR, PDPK1, HRAS, GSK3B, PIK3R1
		3		
hsa05223:Non-small cell lung cancer	6	3.4	0.007073	AKT1, EGFR, FHIT, PDPK1, HRAS, PIK3R1
		3		
hsa05211:Renal cell carcinoma	6	3.4	0.013099	AKT1, HRAS, RAC1, MET, PIK3R1, TGFB2
		3		
hsa00982:Drug metabolism - cytochrome P450	6	3.4	0.015702	GSTM1, GSTA1, GSTM2, GSTA3, GSTT2B, GSTP1
		3		
hsa05218:Melanoma	6	3.4	0.018629	AKT1, EGFR, HRAS, MET, PDGFRB, PIK3R1
		3		
hsa04912:GnRH signaling pathway	6	3.4	0.047342	EGFR, HRAS, MAPK12, MAPK14, MAPK10, SRC
		3		
hsa04750:Inflammatory mediator regulation of TRP channels	6	3.4	0.061428	MAPK12, MAPK14, MAPK10, PPP1CC, PIK3R1, SRC
		3		
hsa04066:HIF-1 signaling pathway	6	3.4	0.061428	AKT1, EGFR, EIF4E, NOS2, INSR, PIK3R1
		3		
hsa00240:Pyrimidine metabolism	6	3.4	0.075202	NME2, DTYMK, DCK, UCK2, PNP, DUT
		3		

hsa05146:Amoebiasis	6	3.4	0.080138	CASP3, ARG2, RAB5A, NOS2, PIK3R1, TGFB2
		3		
hsa01200:Carbon metabolism	6	3.4	0.09874	ALDOA, GPI, ME2, ACADM, GCK, ACAT1
		3		
hsa04670:Leukocyte transendothelial migration	6	3.4	0.113249	RAC2, MAPK12, MAPK14, MMP9, RAC1, PIK3R1
		3		
hsa04650:Natural killer cell mediated cytotoxicity	6	3.4	0.125556	CASP3, HRAS, RAC2, LCK, RAC1, PIK3R1
		3		
hsa04728:Dopaminergic synapse	6	3.4	0.145116	AKT1, MAPK12, MAPK14, GSK3B, MAPK10, PPP1CC
		3		
hsa04550:Signaling pathways regulating pluripotency of stem cells	6	3.4	0.187801	AKT1, HRAS, MAPK12, MAPK14, GSK3B, PIK3R1
		3		
hsa05219:Bladder cancer	5	2.8	0.011584	EGFR, HRAS, MMP9, SRC, DAPK1
		6		
hsa00280:Valine, leucine and isoleucine degradation	5	2.8	0.018467	BCAT2, ACADM, IVD, HADH, ACAT1
		6		
hsa05221:Acute myeloid leukemia	5	2.8	0.032775	AKT1, HRAS, PIM1, KIT, PIK3R1
		6		
hsa05131:Shigellosis	5	2.8	0.049725	MAPK12, MAPK14, RAC1, MAPK10, SRC
		6		
hsa05214:Glioma	5	2.8	0.052126	AKT1, EGFR, HRAS, PDGFRB, PIK3R1

			6			
hsa05133: Pertussis		5	2.8	0.079529	CASP3, MAPK12, MAPK14, MAPK10, NOS2	6
hsa05132: Salmonella infection		5	2.8	0.105673	MAPK12, MAPK14, RAC1, MAPK10, NOS2	6
hsa04922: Glucagon signaling pathway		5	2.8	0.16768	AKT1, GCK, PYGL, PFKFB1, PCK1	6
hsa04110: Cell cycle		5	2.8	0.282657	GSK3B, CHEK1, CCNA2, CDK2, TGFB2	6
hsa04261: Adrenergic signaling in cardiomyocytes		5	2.8	0.391402	AKT1, MAPK12, MAPK14, PPP1CC, PIK3R1	6
hsa04145: Phagosome		5	2.8	0.425874	RAC1, TAP1, RAB5A, EEA1, CTSS	6
hsa04921: Oxytocin signaling pathway		5	2.8	0.450211	EGFR, HRAS, PPP1CC, PIK3R1, SRC	6
hsa05202: Transcriptional misregulation in cancer		5	2.8	0.497843	DOT1L, MMP9, ELANE, MET, MMP3	6
hsa05168: Herpes simplex infection		5	2.8	0.565781	CASP3, TAP1, MAPK10, PPP1CC, CDK2	6
hsa00760: Nicotinate and nicotinamide metabolism		4	2.2	0.024247	NMNAT3, BST1, PNP, NMNAT1	9
hsa00051: Fructose and mannose metabolism		4	2.2	0.031405	ALDOA, SORD, PFKFB1, AKR1B1	9

hsa00500:Starch and sucrose metabolism	4	2.2	0.03401	GPI, GCK, PYGL, AMY2A
hsa00620:Pyruvate metabolism	4	2.2	0.055242	ME2, GLO1, ACAT1, PCK1
hsa04930:Type II diabetes mellitus	4	2.2	0.085498	GCK, MAPK10, INSR, PIK3R1
hsa00330:Arginine and proline metabolism	4	2.2	0.093967	ARG2, NOS2, AMD1, OAT
hsa00310:Lysine degradation	4	2.2	0.102767	DOT1L, HADH, ACAT1, KMT5A
hsa04621:NOD-like receptor signaling pathway	4	2.2	0.11655	HSP90AA1, MAPK12, MAPK14, MAPK10
hsa00140:Steroid hormone biosynthesis	4	2.2	0.130985	AKR1C2, HSD17B1, HSD11B1, SULT2B1
hsa04150:mTOR signaling pathway	4	2.2	0.130985	AKT1, PDPK1, EIF4E, PIK3R1
hsa04210:Apoptosis	4	2.2	0.151142	AKT1, CASP3, APAF1, PIK3R1
hsa04115:p53 signaling pathway	4	2.2	0.17761	CASP3, CHEK1, APAF1, CDK2
hsa00010:Glycolysis / Gluconeogenesis	4	2.2	0.17761	ALDOA, GPI, GCK, PCK1
hsa05140:Leishmaniasis	4	2.2	0.199636	MAPK12, MAPK14, NOS2, TGFB2
hsa05220:Chronic myeloid	4	2.2	0.205243	AKT1, HRAS, PIK3R1, TGFB2

leukemia		9			
hsa01230:Biosynthesis of amino acids	4	2.2	0.216564	ALDOA, BCAT2, ARG2, PAH	9
hsa04612:Antigen processing and presentation	4	2.2	0.228014	HSP90AA1, TAP1, HSPA1A, CTSS	9
hsa05100:Bacterial invasion of epithelial cells	4	2.2	0.239577	RAC1, MET, PIK3R1, SRC	9
hsa04666:Fc gamma R-mediated phagocytosis	4	2.2	0.274797	AKT1, RAC2, RAC1, PIK3R1	9
hsa04540:Gap junction	4	2.2	0.298576	EGFR, HRAS, PDGFRB, SRC	9
hsa04114:Oocyte meiosis	4	2.2	0.423197	AR, AURKA, PPP1CC, CDK2	9
hsa04310:Wnt signaling pathway	4	2.2	0.580519	RAC2, GSK3B, RAC1, MAPK10	9
hsa04630:Jak-STAT signaling pathway	4	2.2	0.614305	AKT1, PIM1, PIK3R1, IL2	9
hsa04022:cGMP-PKG signaling pathway	4	2.2	0.704402	AKT1, PPP1CC, INSR, PIK3R1	9
hsa05010:Alzheimer's disease	4	2.2	0.712092	CASP3, GSK3B, BACE1, APAF1	9
hsa04141:Protein processing in endoplasmic reticulum	4	2.2	0.71588	HSP90AA1, MAN1B1, HSPA1A, MAPK10	9

hsa05034:Alcoholism		4	2.2	0.744814	HRAS, HIST1H4I, PPP1CC, HDAC8
			9		
hsa04020:Calcium signaling pathway		4	2.2	0.751674	EGFR, PDGFRB, NOS2, ITPKA
			9		
hsa00900:Terpenoid biosynthesis	backbone	3	1.7	0.081493	HMGCR, FDPS, ACAT1
			1		
hsa05340:Primary immunodeficiency		3	1.7	0.167849	LCK, TAP1, BTK
			1		
hsa04960:Aldosterone-regulated sodium reabsorption		3	1.7	0.207232	PDPK1, INSR, PIK3R1
			1		
hsa04973:Carbohydrate digestion and absorption		3	1.7	0.231311	AKT1, AMY2A, PIK3R1
			1		
hsa00071:Fatty acid degradation		3	1.7	0.247465	ACADM, HADH, ACAT1
			1		
hsa00983:Drug metabolism - other enzymes		3	1.7	0.263658	UCK2, HPRT1, IMPDH2
			1		
hsa01212:Fatty acid metabolism		3	1.7	0.279857	ACADM, HADH, ACAT1
			1		
hsa05144:Malaria		3	1.7	0.287949	MET, SELE, TGFB2
			1		
hsa05134:Legionellosis		3	1.7	0.328201	CASP3, HSPA1A, APAF1
			1		

hsa04923:Regulation of lipolysis in adipocytes	3	1.7	0.344146	AKT1, INSR, PIK3R1
hsa05416:Viral myocarditis	3	1.7	0.352075	CASP3, RAC2, RAC1
hsa03320:PPAR signaling pathway	3	1.7	0.429219	PDPK1, ACADM, PCK1
hsa04976:Bile secretion	3	1.7	0.444086	SULT2A1, HMGCR, CA2
hsa04920:Adipocytokine signaling pathway	3	1.7	0.451439	AKT1, MAPK10, PCK1
hsa04622:RIG-I-like receptor signaling pathway	3	1.7	0.451439	MAPK12, MAPK14, MAPK10
hsa05323:Rheumatoid arthritis	3	1.7	0.573618	CTSK, MMP3, TGFB2
hsa04972:Pancreatic secretion	3	1.7	0.603891	BST1, RAC1, CA2
hsa04070:Phosphatidylinositol signaling system	3	1.7	0.632525	IMPA1, ITPKA, PIK3R1
hsa04916:Melanogenesis	3	1.7	0.643522	HRAS, GSK3B, KIT
hsa04723:Retrograde endocannabinoid signalling	3	1.7	0.648923	MAPK12, MAPK14, MAPK10

hsa04725:Cholinergic synapse	3	1.7	0.699429	AKT1, HRAS, PIK3R1
		1		
hsa04142:Lysosome	3	1.7	0.743806	CTSK, HEXB, CTSS
		1		
hsa04530:Tight junction	3	1.7	0.803179	AKT1, HRAS, SRC
		1		
hsa04390:Hippo signaling pathway	3	1.7	0.84483	GSK3B, PPP1CC, TGFB2
		1		
hsa04080:Neuroactive ligand-receptor interaction	3	1.7	0.985047	THRA, THRB, F2
		1		

Table S6. The KEGG pathway enrichment analysis for quercetin.

KEGG_PATHWAY	Count	%	pValue	Genes
hsa01100:Metabolic pathways	43	26.22	0.000340773	BCAT2, IMPA1, SORD, NDST1, PNMT, HSD17B1, DTYMK, HEXB, DCK, ADH5, HK1, PAH, HPRT1, AKR1C3, TYMS, CBR1, NT5M, ATIC, DHODH, SPR, UCK2, IMPDH2, UAP1, BST1, AK1, OTC, APRT, PCK1, GART, GPI, UMPS, DHFR, GCK, RFK, ADK, AKR1B1, BHMT, HSD11B1, MTAP, ABO, NMNAT1, DUT, CBS
hsa05200:Pathways in cancer	23	14.02	1.44E-05	FGFR1, AR, HRAS, HSP90AA1, MAP2K1, MET, BIRC7, CDK6, MAPK10, KIT, MMP1, CDK2, DAPK1, CDC42, CASP3, NCOA4, GSK3B, RHOA, PDGFRB, MAPK8, ABL1, PIK3R1, AKT2
hsa04151:PI3K-Akt signaling pathway	21	12.8	2.23E-05	FGFR1, HRAS, HSP90AA1, MAP2K1, MET, CDK6, KIT, CDK2, EPHA2, KDR, PCK1, PDPK1, GSK3B, TEK, RHEB, PDGFRB, JAK2, INSR, PIK3R1, AKT2, IL2
hsa04014:Ras signaling pathway	20	12.2	1.45E-07	FGFR1, HRAS, MAP2K1, MET, MAPK10, KIT, EPHA2, KDR, CDC42, TEK, RHOA, ZAP70, RAB5A, PDGFRB, MAPK8, ABL1, INSR, RASA1, PIK3R1, AKT2
hsa05205:Proteoglycans in cancer	17	10.37	2.91E-06	FGFR1, HRAS, MAP2K1, MET, ESR1, PPP1CC, SRC, KDR, CDC42, PDPK1, CASP3, MAPK12, MAPK14, RHOA, PIK3R1, PLAU, AKT2

hsa04015:Rap1 pathway	signaling	17	10.37	5.50E-06	FGFR1, HRAS, MAP2K1, MET, KIT, EPHA2, SRC, KDR, CDC42, MAPK12, MAPK14, TEK, RHOA, PDGFRB, INSR, PIK3R1, AKT2
hsa04910:Insulin pathway	signaling	15	9.15	7.50E-07	HRAS, MAP2K1, HK1, MAPK10, PPP1CC, PCK1, PDPK1, GSK, GSK3B, RHEB, MAPK8, PTPN1, INSR, PIK3R1, AKT2
hsa04510:Focal adhesion		15	9.15	7.79E-05	HRAS, MAP2K1, MET, MAPK10, PPP1CC, SRC, KDR, CDC42, PDPK1, GSK3B, RHOA, PDGFRB, MAPK8, PIK3R1, AKT2
hsa04010:MAPK pathway	signaling	15	9.15	0.000712811	FGFR1, HRAS, MAP2K1, HSPA1A, MAPKAPK2, MAPK10, CDC42, CASP3, MAPK12, MAPK14, PDGFRB, MAPK8, RASA1, HSPA8, AKT2
hsa04917:Prolactin pathway	signaling	14	8.54	1.41E-09	HRAS, MAP2K1, ESR1, MAPK10, ESR2, SRC, GSK, MAPK12, MAPK14, GSK3B, MAPK8, JAK2, PIK3R1, AKT2
hsa04722:Neurotrophin signaling pathway		14	8.54	8.96E-07	CDC42, PDPK1, HRAS, MAPK12, MAP2K1, MAPK14, GSK3B, RHOA, MAPK8, MAPK10, MAPKAPK2, ABL1, PIK3R1, AKT2
hsa00230:Purine metabolism		14	8.54	6.06E-05	GMPT2, AK1, DCK, PDE4D, HPRT1, GMPR, APRT, GART, NT5M, ATIC, ADK, PDE4B, PDE5A, IMPDH2
hsa04660:T cell receptor signaling pathway		13	7.93	1.10E-06	CDC42, PDPK1, HRAS, MAPK12, MAP2K1, MAPK14, GSK3B, LCK, RHOA, ZAP70, PIK3R1, AKT2, IL2
hsa05152:Tuberculosis		13	7.93	0.000263824	VDR, CASP3, MAPK12, MAPK14, RHOA, RAB5A, EEA1, JAK2, MAPK8, MAPK10, APAF1, SRC, AKT2
hsa05145:Toxoplasmosis		12	7.32	2.73E-05	PDPK1, CASP3, MAPK12, MAPK14, BIRC7, MAPK8, HSPA1A, JAK2, MAPK10, PIK3R1, HSPA8, AKT2

hsa04068:FoxO signaling pathway	12	7.32	8.87E-05	PDPK1, HRAS, MAPK12, MAP2K1, MAPK14, MAPK8, MAPK10, INSR, PIK3R1, CDK2, AKT2, PCK1
hsa05161:Hepatitis B	12	7.32	0.000180104	CASP3, HRAS, MAP2K1, MAPK8, CDK6, APAF1, MAPK10, CCNA2, PIK3R1, SRC, CDK2, AKT2
hsa05164:Influenza A	12	7.32	0.000860567	MAPK12, MAP2K1, MAPK14, GSK3B, MAPK8, HSPA1A, JAK2, MAPK10, CASP1, PIK3R1, HSPA8, AKT2
hsa05203:Viral carcinogenesis	12	7.32	0.003194488	CDC42, CASP3, HRAS, RHOA, CHEK1, CDK6, MAPKAPK2, CCNA2, HDAC8, PIK3R1, SRC, CDK2
hsa01130:Biosynthesis of antibiotics	12	7.32	0.00412817	GPI, UAP1, BCAT2, GCK, ATIC, OTC, AK1, ADH5, HK1, GART, CBS, PCK1
hsa04144:Endocytosis	12	7.32	0.016868028	CDC42, HRAS, MET, RAB5A, RHOA, RAB11A, EEA1, HSPA1A, KIT, SRC, HSPA8, KDR
hsa00980:Metabolism of xenobiotics by cytochrome P450	11	6.71	2.29E-06	GSTM1, GSTA1, GSTM2, AKR1C2, GSTA3, CBR1, GSTT2B, HSD11B1, ADH5, GSTP1, AKR1C1
hsa05215:Prostate cancer	11	6.71	1.12E-05	FGFR1, AR, PDPK1, HRAS, HSP90AA1, MAP2K1, GSK3B, PDGFRB, PIK3R1, CDK2, AKT2
hsa04931:Insulin resistance	11	6.71	6.80E-05	PPARA, PDPK1, GSK3B, MAPK8, PTPN1, MAPK10, PPP1CC, INSR, PIK3R1, AKT2, PCK1
hsa04919:Thyroid hormone signaling pathway	11	6.71	0.000107616	PDPK1, NCOA1, HRAS, NCOA2, MAP2K1, GSK3B, ESR1, RHEB, PIK3R1, SRC, AKT2
hsa05169:Epstein-Barr virus infection	11	6.71	0.005590177	MAPK12, MAPK14, GSK3B, MAPK8, HSPA1A, MAPK10, CCNA2, PIK3R1, HSPA8, CDK2, AKT2
hsa04370:VEGF signaling pathway	10	6.1	3.55E-06	CDC42, HRAS, MAPK12, MAP2K1, MAPK14, MAPKAPK2, PIK3R1, SRC, KDR, AKT2

hsa05230:Central metabolism in cancer	carbon	10	6.1	5.34E-06	FGFR1, HRAS, GCK, MAP2K1, MET, PDGFRB, HK1, KIT, PIK3R1, AKT2	
hsa04664:Fc signaling pathway	epsilon	RI	10	6.1	8.92E-06	PDPK1, HRAS, MAPK12, MAP2K1, MAPK14, MAPK8, MAPK10, PIK3R1, AKT2, BTK
hsa05204:Chemical carcinogenesis			10	6.1	3.40E-05	GSTM1, GSTA1, GSTM2, GSTA3, CBR1, GSTT2B, SULT1A1, HSD11B1, ADH5, GSTP1
hsa04914:Progesterone-medi- ated oocyte maturation			10	6.1	6.67E-05	HSP90AA1, MAPK12, MAP2K1, MAPK14, MAPK8, MAPK10, CCNA2, PIK3R1, CDK2, AKT2
hsa04915:Estrogen pathway	signaling		10	6.1	0.000182626	HRAS, HSP90AA1, MAP2K1, ESR1, HSPA1A, ESR2, PIK3R1, SRC, HSPA8, AKT2
hsa04668:TNF pathway	signaling		10	6.1	0.000306781	CASP3, MAPK12, MAP2K1, MAPK14, MAPK8, MAPK10, MMP3, SELE, PIK3R1, AKT2
hsa04071:Sphingolipid signaling pathway			10	6.1	0.00076618	PDPK1, HRAS, MAPK12, MAP2K1, MAPK14, RHOA, MAPK8, MAPK10, PIK3R1, AKT2
hsa04380:Osteoclast differentiation			10	6.1	0.00143165	CTSK, MAPK12, MAP2K1, MAPK14, LCK, MAPK8, MAPK10, PIK3R1, AKT2, BTK
hsa05162:Measles			10	6.1	0.001591842	RAB9A, GSK3B, CDK6, HSPA1A, JAK2, PIK3R1, HSPA8, CDK2, AKT2, IL2
hsa05160:Hepatitis C			10	6.1	0.001591842	PPARA, PDPK1, HRAS, MAPK12, MAPK14, GSK3B, MAPK8, MAPK10, PIK3R1, AKT2
hsa04062:Chemokine pathway	signaling		10	6.1	0.014153225	CDC42, HRAS, MAP2K1, HCK, GSK3B, RHOA, JAK2, PIK3R1, SRC, AKT2
hsa04024:cAMP pathway	signaling		10	6.1	0.020471649	PPARA, MAP2K1, PDE4B, RHOA, MAPK8, PDE4D, MAPK10, PPP1CC, PIK3R1, AKT2
hsa04810:Regulation of actin cytoskeleton			10	6.1	0.029389537	CDC42, FGFR1, HRAS, MAP2K1, F2, RHOA, PDGFRB, PPP1CC, PIK3R1, SRC

hsa05206:MicroRNAs in cancer	10	6.1	0.131633155	CASP3, HRAS, MAP2K1, MET, PIM1, RHOA, PDGFRB, CDK6, ABL1, PLAU
hsa04012:ErbB signaling pathway	9	5.49	0.000388185	HRAS, MAP2K1, GSK3B, MAPK8, MAPK10, ABL1, PIK3R1, SRC, AKT2
hsa05231:Choline metabolism in cancer	9	5.49	0.001054924	PDPK1, HRAS, MAP2K1, PDGFRB, RHEB, MAPK8, MAPK10, PIK3R1, AKT2
hsa04611:Platelet activation	9	5.49	0.005155012	FGG, MAPK12, MAPK14, RHOA, PPP1CC, PIK3R1, SRC, AKT2, BTK
hsa04550:Signaling pathways regulating pluripotency of stem cells	9	5.49	0.007987844	FGFR1, HRAS, MAPK12, MAP2K1, MAPK14, GSK3B, JAK2, PIK3R1, AKT2
hsa04932:Non-alcoholic fatty liver disease (NAFLD)	9	5.49	0.012311847	CDC42, PPARA, CASP3, GSK3B, MAPK8, MAPK10, INSR, PIK3R1, AKT2
hsa05210:Colorectal cancer	8	4.88	0.000255348	CASP3, MAP2K1, GSK3B, RHOA, MAPK8, MAPK10, PIK3R1, AKT2
hsa05120:Epithelial cell signaling in Helicobacter pylori infection	8	4.88	0.000414565	CDC42, CASP3, MAPK12, MAPK14, MET, MAPK8, MAPK10, SRC
hsa05218:Melanoma	8	4.88	0.000592128	FGFR1, HRAS, MAP2K1, MET, PDGFRB, CDK6, PIK3R1, AKT2
hsa04912:GnRH signaling pathway	8	4.88	0.002564025	CDC42, HRAS, MAPK12, MAP2K1, MAPK14, MAPK8, MAPK10, SRC
hsa00240:Pyrimidine metabolism	8	4.88	0.005398534	TYMS, UMPS, NT5M, DTYMK, DHODH, DCK, UCK2, DUT
hsa04620:Toll-like receptor signaling pathway	8	4.88	0.005987073	CTSK, MAPK12, MAP2K1, MAPK14, MAPK8, MAPK10, PIK3R1, AKT2

hsa04152:AMPK pathway	signaling	8	4.88	0.012562023	PDPK1, PFKFB1, RHEB, CCNA2, INSR, PIK3R1, AKT2, PCK1
hsa04360:Axon guidance		8	4.88	0.015405725	CDC42, HRAS, GSK3B, MET, RHOA, ABL1, RASA1, EPHA2
hsa05166:HTLV-I infection		8	4.88	0.273422172	HRAS, GSK3B, LCK, PDGFRB, CHEK1, PIK3R1, AKT2, IL2
hsa00480:Glutathione metabolism		7	4.27	0.000570012	GSTM1, GSTA1, GSTM2, GSR, GSTA3, GSTT2B, GSTP1
hsa05131:Shigellosis		7	4.27	0.001907553	CDC42, MAPK12, MAPK14, MAPK8, MAPK10, ABL1, SRC
hsa05212:Pancreatic cancer		7	4.27	0.002066618	CDC42, MAP2K1, MAPK8, CDK6, MAPK10, PIK3R1, AKT2
hsa00982:Drug metabolism cytochrome P450	-	7	4.27	0.002604333	GSTM1, GSTA1, GSTM2, GSTA3, GSTT2B, ADH5, GSTP1
hsa04520:Adherens junction		7	4.27	0.003240941	CDC42, FGFR1, MET, RHOA, PTPN1, INSR, SRC
hsa05133:Pertussis		7	4.27	0.004262009	CASP3, MAPK12, MAPK14, RHOA, MAPK8, MAPK10, CASP1
hsa04750:Inflammatory mediator regulation of TRP channels		7	4.27	0.015198484	MAPK12, MAPK14, MAPK8, MAPK10, PPP1CC, PIK3R1, SRC
hsa05142:Chagas disease (American trypanosomiasis)	disease	7	4.27	0.019839336	MAPK12, MAPK14, MAPK8, MAPK10, PIK3R1, AKT2, IL2
hsa04728:Dopaminergic synapse		7	4.27	0.047796866	MAPK12, MAPK14, GSK3B, MAPK8, MAPK10, PPP1CC, AKT2
hsa04022:cGMP-PKG pathway	signaling	7	4.27	0.126287487	MAP2K1, PDE5A, RHOA, PPP1CC, INSR, PIK3R1, AKT2

hsa05168:Herpes simplex infection	7	4.27	0.17428061	CASP3, TAP1, MAPK8, JAK2, MAPK10, PPP1CC, CDK2
hsa04930:Type II diabetes mellitus	6	3.66	0.002874284	GCK, HK1, MAPK8, MAPK10, INSR, PIK3R1
hsa05014:Amyotrophic lateral sclerosis (ALS)	6	3.66	0.003441934	CASP3, MAPK12, MAPK14, RAB5A, APAF1, CASP1
hsa05213:Endometrial cancer	6	3.66	0.004086067	PDPK1, HRAS, MAP2K1, GSK3B, PIK3R1, AKT2
hsa04621:NOD-like receptor signaling pathway	6	3.66	0.005207541	HSP90AA1, MAPK12, MAPK14, MAPK8, MAPK10, CASP1
hsa05221:Acute myeloid leukemia	6	3.66	0.005625459	HRAS, MAP2K1, PIM1, KIT, PIK3R1, AKT2
hsa05223:Non-small cell lung cancer	6	3.66	0.005625459	PDPK1, HRAS, MAP2K1, CDK6, PIK3R1, AKT2
hsa00140:Steroid hormone biosynthesis	6	3.66	0.006531403	AKR1C3, AKR1C2, HSD17B1, HSD11B1, SULT2B1, AKR1C1
hsa05211:Renal cell carcinoma	6	3.66	0.010505314	CDC42, HRAS, MAP2K1, MET, PIK3R1, AKT2
hsa05214:Glioma	6	3.66	0.010505314	HRAS, MAP2K1, PDGFRB, CDK6, PIK3R1, AKT2
hsa04662:B cell receptor signaling pathway	6	3.66	0.013394653	HRAS, MAP2K1, GSK3B, PIK3R1, AKT2, BTK
hsa04920:Adipocytokine signaling pathway	6	3.66	0.014192927	PPARA, MAPK8, JAK2, MAPK10, AKT2, PCK1
hsa05220:Chronic myeloid leukemia	6	3.66	0.015884239	HRAS, MAP2K1, CDK6, ABL1, PIK3R1, AKT2
hsa05132:Salmonella infection	6	3.66	0.027596158	CDC42, MAPK12, MAPK14, MAPK8, MAPK10, CASP1

hsa05222:Small cell lung cancer	6	3.66	0.030188985	BIRC7, CDK6, APAF1, PIK3R1, CDK2, AKT2
hsa04066:HIF-1 signaling pathway	6	3.66	0.050745315	MAP2K1, TEK, HK1, INSR, PIK3R1, AKT2
hsa04650:Natural killer cell mediated cytotoxicity	6	3.66	0.105874492	CASP3, HRAS, MAP2K1, LCK, ZAP70, PIK3R1
hsa04110:Cell cycle	6	3.66	0.111437834	GSK3B, CHEK1, CDK6, ABL1, CCNA2, CDK2
hsa04921:Oxytocin signaling pathway	6	3.66	0.224723755	HRAS, MAP2K1, RHOA, PPP1CC, PIK3R1, SRC
hsa04141:Protein processing in endoplasmic reticulum	6	3.66	0.26710988	HSP90AA1, BAG1, MAPK8, HSPA1A, MAPK10, HSPA8
hsa05219:Bladder cancer	5	3.05	0.009603085	HRAS, MAP2K1, SRC, MMP1, DAPK1
hsa00520:Amino sugar and nucleotide sugar metabolism	5	3.05	0.01652896	GPI, UAP1, GCK, HEXB, HK1
hsa05134:Legionellosis	5	3.05	0.024457365	CASP3, HSPA1A, APAF1, CASP1, HSPA8
hsa00010:Glycolysis / Gluconeogenesis	5	3.05	0.048435003	GPI, GCK, ADH5, HK1, PCK1
hsa04115:p53 signaling pathway	5	3.05	0.048435003	CASP3, CHEK1, CDK6, APAF1, CDK2
hsa03320:PPAR signaling pathway	5	3.05	0.048435003	PPARA, PDPK1, FABP4, MMP1, PCK1
hsa05100:Bacterial invasion of epithelial cells	5	3.05	0.076097284	CDC42, MET, RHOA, PIK3R1, SRC
hsa04666:Fc gamma R-mediated phagocytosis	5	3.05	0.093913818	CDC42, MAP2K1, HCK, PIK3R1, AKT2

hsa04922:Glucagon signaling pathway	5	3.05	0.145974746	PPARA, GCK, PFKFB1, AKT2, PCK1
hsa04114:Oocyte meiosis	5	3.05	0.185715469	AR, MAP2K1, AURKA, PPP1CC, CDK2
hsa04725:Cholinergic synapse	5	3.05	0.194059066	HRAS, MAP2K1, JAK2, PIK3R1, AKT2
hsa04670:Leukocyte transendothelial migration	5	3.05	0.2241284	CDC42, MAPK12, MAPK14, RHOA, PIK3R1
hsa04530:Tight junction	5	3.05	0.310567539	CDC42, HRAS, RHOA, SRC, AKT2
hsa04630:Jak-STAT signaling pathway	5	3.05	0.348066889	PIM1, JAK2, PIK3R1, AKT2, IL2
hsa04261:Adrenergic signaling in cardiomyocytes	5	3.05	0.352768104	MAPK12, MAPK14, PPP1CC, PIK3R1, AKT2
hsa05010:Alzheimer's disease	5	3.05	0.455241776	CASP3, GSK3B, BACE1, MME, APAF1
hsa05034:Alcoholism	5	3.05	0.495796526	HRAS, MAP2K1, PPP1CC, HDAC8, PKIA
hsa04060:Cytokine-cytokine receptor interaction	5	3.05	0.701793794	MET, PDGFRB, KIT, KDR, IL2
hsa00670:One carbon pool by folate	4	2.44	0.00749634	TYMS, DHFR, ATIC, GART
hsa00051:Fructose and mannose metabolism	4	2.44	0.027281939	SORD, PFKFB1, AKR1B1, HK1
hsa05340:Primary immunodeficiency	4	2.44	0.031956097	LCK, TAP1, ZAP70, BTK
hsa04960:Aldosterone-regulated sodium reabsorption	4	2.44	0.045342186	PDPK1, NR3C2, INSR, PIK3R1
hsa00983:Drug metabolism other enzymes	- 4	2.44	0.06798725	UMPS, UCK2, HPRT1, IMPDH2

hsa04923:Regulation of lipolysis in adipocytes	4	2.44	0.107414442	FABP4, INSR, PIK3R1, AKT2
hsa04150:mTOR signaling pathway	4	2.44	0.116176987	PDPK1, RHEB, PIK3R1, AKT2
hsa04210:Apoptosis	4	2.44	0.134466481	CASP3, APAF1, PIK3R1, AKT2
hsa04610:Complement and coagulation cascades	4	2.44	0.168621577	F11, FGG, F2, PLAU
hsa04622:RIG-I-like receptor signaling pathway	4	2.44	0.173694917	MAPK12, MAPK14, MAPK8, MAPK10
hsa01230:Biosynthesis of amino acids	4	2.44	0.194401323	BCAT2, OTC, PAH, CBS
hsa04612:Antigen processing and presentation	4	2.44	0.20497765	HSP90AA1, TAP1, HSPA1A, HSPA8
hsa04064:NF-kappa B signaling pathway	4	2.44	0.265120167	LCK, ZAP70, PLAU, BTK
hsa05323:Rheumatoid arthritis	4	2.44	0.270708151	CTSK, TEK, MMP3, MMP1
hsa04540:Gap junction	4	2.44	0.270708151	HRAS, MAP2K1, PDGFRB, SRC
hsa04972:Pancreatic secretion	4	2.44	0.298821122	BST1, RHOA, RAB11A, CA2
hsa04916:Melanogenesis	4	2.44	0.338414923	HRAS, MAP2K1, GSK3B, KIT
hsa04723:Retrograde endocannabinoid signaling	4	2.44	0.344071398	MAPK12, MAPK14, MAPK8, MAPK10
hsa01200:Carbon metabolism	4	2.44	0.411366851	GPI, GCK, ADH5, HK1
hsa04310:Wnt signaling pathway	4	2.44	0.543068013	GSK3B, RHOA, MAPK8, MAPK10

hsa05202:Transcriptional misregulation in cancer	4	2.44	0.676455682	ELANE, MET, MMP3, PLAU
hsa00760:Nicotinate and nicotinamide metabolism	3	1.83	0.118870284	NT5M, BST1, NMNAT1
hsa05216:Thyroid cancer	3	1.83	0.118870284	HRAS, MAP2K1, NCOA4
hsa00052:Galactose metabolism	3	1.83	0.125717971	GCK, AKR1B1, HK1
hsa00500:Starch and sucrose metabolism	3	1.83	0.14678674	GPI, GCK, HK1
hsa00270:Cysteine and methionine metabolism	3	1.83	0.183284376	BHMT, MTAP, CBS
hsa04973:Carbohydrate digestion and absorption	3	1.83	0.213332617	HK1, PIK3R1, AKT2
hsa04961:Endocrine and other factor-regulated calcium reabsorption	3	1.83	0.236164348	VDR, ESR1, RAB11A
hsa04913:Ovarian steroidogenesis	3	1.83	0.266790581	AKR1C3, HSD17B1, INSR
hsa05130:Pathogenic Escherichia coli infection	3	1.83	0.28211772	CDC42, RHOA, ABL1
hsa04720:Long-term potentiation	3	1.83	0.394844465	HRAS, MAP2K1, PPP1CC
hsa05140:Leishmaniasis	3	1.83	0.430766143	MAPK12, MAPK14, JAK2
hsa05146:Amoebiasis	3	1.83	0.645350482	CASP3, RAB5A, PIK3R1
hsa04726:Serotonergic synapse	3	1.83	0.67024668	CASP3, HRAS, MAP2K1

hsa04270:Vascular muscle contraction	smooth	3	1.83	0.70714025	MAP2K1, RHOA, PPP1CC
hsa04145:Phagosome		3	1.83	0.827590169	TAP1, RAB5A, EEA1

Table S7. The KEGG pathway enrichment analysis for EGCG.

KEGG_PATHWAY	Count	Percentage (%)	pValue	Genes
hsa01100:Metabolic pathways	44	29.53	8.15E-06	BCAT2, IMPA1, SORD, PNMT, HMGCR, HSD17B1, DTYMK, DCK, ADH5, HK1, LSS, PAH, HPRT1, AKR1C3, TYMS, NT5M, DHODH, SPR, UCK2, HADH, AMD1, AMY2A, HPGDS, UAP1, FECH, BST1, PCK1, GART, NME2, DHFR, GCK, RFK, PYGL, ADK, AKR1B1, BHMT, PLA2G2A, HSD11B1, MTAP, LTA4H, OAT, ABO, NMNAT1, DUT
hsa05200:Pathways in cancer	19	12.75	0.000276	HSP90AB1, FGFR1, AR, HRAS, PPARD, HSP90AA1, RXRB, RXRA, TGFBR1, MET, MAPK10, MMP1, CDK2, DAPK1, MAPK1, CASP3, GSK3B, RARB, AKT2
hsa04151:PI3K-Akt signaling pathway	18	12.08	0.000174	HSP90AB1, FGFR1, HRAS, HSP90AA1, RXRA, MET, CDK2, EPHA2, KDR, PCK1, MAPK1, PDPK1, GSK3B, TEK, JAK2, INSR, AKT2, SYK
hsa04919:Thyroid hormone signaling pathway	13	8.72	9.94E-07	MAPK1, PDPK1, NCOA1, HRAS, THRA, NCOA2, THRB, RXRB, GSK3B, RXRA, ESR1, SRC, AKT2
hsa04910:Insulin signaling pathway	13	8.72	7.54E-06	HRAS, HK1, MAPK10, PPP1CC, PCK1, MAPK1, PDPK1, GCK, PYGL, GSK3B, PTPN1, INSR, AKT2

hsa04014:Ras signaling pathway	13	8.72	0.000867	FGFR1, HRAS, MET, MAPK10, EPHA2, KDR, MAPK1, TEK, ZAP70, PLA2G2A, RAB5A, INSR, AKT2
hsa04931:Insulin resistance	12	8.05	3.99E-06	NR1H2, PPARA, PDPK1, PYGL, GSK3B, PTPN1, MAPK10, PPP1CC, INSR, AKT2, PCK1, NR1H3
hsa05152:Tuberculosis	12	8.05	0.000385	MAPK1, VDR, CASP3, MAPK14, CD209, RAB5A, EEA1, JAK2, MAPK10, SRC, AKT2, SYK
hsa05205:Proteoglycans in cancer	12	8.05	0.001073	MAPK1, FGFR1, PDPK1, CASP3, HRAS, MAPK14, MET, ESR1, PPP1CC, SRC, KDR, AKT2
hsa01130:Biosynthesis of antibiotics	12	8.05	0.001719	UAP1, NME2, BCAT2, GCK, HMGCR, ADH5, HK1, LSS, HADH, OAT, GART, PCK1
hsa04015:Rap1 signaling pathway	11	7.38	0.00513	MAPK1, FGFR1, HRAS, MAPK14, TEK, MET, INSR, SRC, EPHA2, KDR, AKT2
hsa03320:PPAR signaling pathway	10	6.71	3.13E-06	PPARA, PDPK1, PPARD, RXRB, RXRA, FABP7, MMP1, FABP6, PCK1, NR1H3
hsa04917:Prolactin signaling pathway	10	6.71	5.13E-06	MAPK1, HRAS, GCK, MAPK14, GSK3B, ESR1, JAK2, MAPK10, SRC, AKT2
hsa05215:Prostate cancer	10	6.71	3.03E-05	HSP90AB1, MAPK1, FGFR1, AR, PDPK1, HRAS, HSP90AA1, GSK3B, CDK2, AKT2
hsa05160:Hepatitis C	10	6.71	0.00072	MAPK1, PPARA, PDPK1, HRAS, MAPK14, RXRA, GSK3B, MAPK10, AKT2, NR1H3
hsa04068:FoxO signaling pathway	10	6.71	0.00076	MAPK1, PDPK1, HRAS, MAPK14, TGFBR1, MAPK10, INSR, CDK2, AKT2, PCK1

hsa00230:Purine metabolism	10	6.71	0.004956	NME2, GMPR2, NT5M, ADK, PDE4B, PDE5A, DCK, PDE4D, HPRT1, GART
hsa04510:Focal adhesion	10	6.71	0.013318	MAPK1, PDPK1, HRAS, GSK3B, MET, MAPK10, PPP1CC, SRC, KDR, AKT2
hsa05204:Chemical carcinogenesis	9	6.04	9.98E-05	GSTM1, GSTA1, GSTM2, GSTA3, SULT2A1, SULT1A1, HSD11B1, ADH5, GSTP1
hsa04914:Progesterone-mediated oocyte maturation	9	6.04	0.000181	HSP90AB1, PGR, MAPK1, HSP90AA1, MAPK14, MAPK10, CCNA2, CDK2, AKT2
hsa04660:T cell receptor signaling pathway	9	6.04	0.000576	ITK, MAPK1, PDPK1, HRAS, MAPK14, GSK3B, LCK, ZAP70, AKT2
hsa05161:Hepatitis B	9	6.04	0.005079	MAPK1, CASP3, HRAS, TGFBR1, MAPK10, CCNA2, SRC, CDK2, AKT2
hsa04010:MAPK signaling pathway	9	6.04	0.096831	MAPK1, FGFR1, CASP3, HRAS, MAPK14, TGFBR1, MAPK10, MAPKAPK2, AKT2
hsa00980:Metabolism of xenobiotics by cytochrome P450	8	5.37	0.000389	GSTM1, GSTA1, GSTM2, GSTA3, SULT2A1, HSD11B1, ADH5, GSTP1
hsa00240:Pyrimidine metabolism	8	5.37	0.002914	TYMS, NME2, NT5M, DTYMK, DHODH, DCK, UCK2, DUT
hsa04722:Neurotrophin signaling pathway	8	5.37	0.006413	MAPK1, PDPK1, HRAS, MAPK14, GSK3B, MAPK10, MAPKAPK2, AKT2
hsa04380:Osteoclast differentiation	8	5.37	0.010199	MAPK1, CTSK, MAPK14, TGFBR1, LCK, MAPK10, AKT2, SYK
hsa04932:Non-alcoholic fatty liver disease (NAFLD)	8	5.37	0.020895	PPARA, CASP3, RXRA, GSK3B, MAPK10, INSR, AKT2, NR1H3
hsa05203:Viral carcinogenesis	8	5.37	0.082908	MAPK1, CASP3, HRAS, MAPKAPK2, CCNA2, SRC, CDK2, SYK

hsa05223:Non-small cell lung cancer	7	4.7	0.000524	MAPK1, PDPK1, HRAS, RXRB, RXRA, RARB, AKT2
hsa04370:VEGF signaling pathway	7	4.7	0.000832	MAPK1, HRAS, MAPK14, MAPKAPK2, SRC, KDR, AKT2
hsa05230:Central carbon metabolism in cancer	7	4.7	0.001074	MAPK1, FGFR1, HRAS, GCK, MET, HK1, AKT2
hsa04664:Fc epsilon RI signaling pathway	7	4.7	0.001476	MAPK1, PDPK1, HRAS, MAPK14, MAPK10, AKT2, SYK
hsa04920:Adipocytokine signaling pathway	7	4.7	0.001717	PPARA, RXRB, RXRA, JAK2, MAPK10, AKT2, PCK1
hsa04520:Adherens junction	7	4.7	0.001847	MAPK1, FGFR1, TGFBR1, MET, PTPN1, INSR, SRC
hsa04915:Estrogen signaling pathway	7	4.7	0.009535	HSP90AB1, MAPK1, HRAS, HSP90AA1, ESR1, SRC, AKT2
hsa05145:Toxoplasmosis	7	4.7	0.02119	MAPK1, PDPK1, CASP3, MAPK14, JAK2, MAPK10, AKT2
hsa04611:Platelet activation	7	4.7	0.032161	MAPK1, FGG, MAPK14, PPP1CC, SRC, AKT2, SYK
hsa04550:Signaling pathways regulating pluripotency of stem cells	7	4.7	0.04372	MAPK1, FGFR1, HRAS, MAPK14, GSK3B, JAK2, AKT2
hsa05164:Influenza A	7	4.7	0.100629	MAPK1, MAPK14, GSK3B, JAK2, MAPK10, CASP1, AKT2
hsa04062:Chemokine signaling pathway	7	4.7	0.127135	ITK, MAPK1, HRAS, GSK3B, JAK2, SRC, AKT2

hsa05169:Epstein-Barr virus infection	7	4.7	0.136664	MAPK14, GSK3B, MAPK10, CCNA2, CDK2, AKT2, SYK
hsa04024:cAMP signaling pathway	7	4.7	0.156698	MAPK1, PPARA, PDE4B, PDE4D, MAPK10, PPP1CC, AKT2
hsa04144:Endocytosis	7	4.7	0.337461	HRAS, TGFBR1, MET, RAB5A, EEA1, SRC, KDR
hsa04621:NOD-like receptor signaling pathway	6	4.03	0.003233	HSP90AB1, MAPK1, HSP90AA1, MAPK14, MAPK10, CASP1
hsa05210:Colorectal cancer	6	4.03	0.005431	MAPK1, CASP3, TGFBR1, GSK3B, MAPK10, AKT2
hsa00982:Drug metabolism - cytochrome P450	6	4.03	0.008019	GSTM1, GSTA1, GSTM2, GSTA3, ADH5, GSTP1
hsa04012:ErbB signaling pathway	6	4.03	0.021602	MAPK1, HRAS, GSK3B, MAPK10, SRC, AKT2
hsa04668:TNF signaling pathway	6	4.03	0.045134	MAPK1, CASP3, MAPK14, MAPK10, MMP3, AKT2
hsa04114:Oocyte meiosis	6	4.03	0.049855	PGR, MAPK1, AR, AURKA, PPP1CC, CDK2
hsa04071:Sphingolipid signaling pathway	6	4.03	0.069573	MAPK1, PDPK1, HRAS, MAPK14, MAPK10, AKT2
hsa04650:Natural killer cell mediated cytotoxicity	6	4.03	0.073563	MAPK1, CASP3, HRAS, LCK, ZAP70, SYK
hsa04152:AMPK signaling pathway	6	4.03	0.073563	PDPK1, HMGCR, CCNA2, INSR, AKT2, PCK1
hsa05168:Herpes simplex infection	6	4.03	0.24628	CASP3, TAP1, JAK2, MAPK10, PPP1CC, CDK2
hsa04810:Regulation of actin cytoskeleton	6	4.03	0.346669	MAPK1, FGFR1, HRAS, F2, PPP1CC, SRC
hsa05219:Bladder cancer	5	3.36	0.006516	MAPK1, HRAS, SRC, MMP1, DAPK1

hsa04930:Type II diabetes mellitus	5	3.36	0.011347	MAPK1, GCK, HK1, MAPK10, INSR
hsa00480:Glutathione metabolism	5	3.36	0.013974	GSTM1, GSTA1, GSTM2, GSTA3, GSTP1
hsa05213:Endometrial cancer	5	3.36	0.014928	MAPK1, PDPK1, HRAS, GSK3B, AKT2
hsa05221:Acute myeloid leukemia	5	3.36	0.019152	MAPK1, PPARD, HRAS, PIM1, AKT2
hsa05120:Epithelial cell signaling in Helicobacter pylori infection	5	3.36	0.0343	CASP3, MAPK14, MET, MAPK10, SRC
hsa04662:B cell receptor signaling pathway	5	3.36	0.037631	MAPK1, HRAS, GSK3B, AKT2, SYK
hsa05218:Melanoma	5	3.36	0.041141	MAPK1, FGFR1, HRAS, MET, AKT2
hsa05133:Pertussis	5	3.36	0.048701	MAPK1, CASP3, MAPK14, MAPK10, CASP1
hsa05222:Small cell lung cancer	5	3.36	0.070721	RXRΒ, RXRA, RARB, CDK2, AKT2
hsa04912:GnRH signaling pathway	5	3.36	0.086008	MAPK1, HRAS, MAPK14, MAPK10, SRC
hsa04066:HIF-1 signaling pathway	5	3.36	0.105698	MAPK1, TEK, HK1, INSR, AKT2
hsa04922:Glucagon signaling pathway	5	3.36	0.108666	PPARA, GCK, PYGL, AKT2, PCK1
hsa05231:Choline metabolism in cancer	5	3.36	0.114714	MAPK1, PDPK1, HRAS, MAPK10, AKT2
hsa05142:Chagas disease (American trypanosomiasis)	5	3.36	0.124059	MAPK1, MAPK14, TGFBR1, MAPK10, AKT2
hsa04620:Toll-like receptor signaling pathway	5	3.36	0.130465	MAPK1, CTSK, MAPK14, MAPK10, AKT2
hsa04360:Axon guidance	5	3.36	0.205029	MAPK1, HRAS, GSK3B, MET, EPHA2
hsa04728:Dopaminergic synapse	5	3.36	0.20886	MAPK14, GSK3B, MAPK10, PPP1CC, AKT2
hsa05162:Measles	5	3.36	0.228314	GSK3B, CD209, JAK2, CDK2, AKT2

hsa04022:cGMP-PKG signaling pathway	5	3.36	0.364359	MAPK1, PDE5A, PPP1CC, INSR, AKT2
hsa05010:Alzheimer's disease	5	3.36	0.372768	MAPK1, CASP3, GSK3B, BACE1, MME
hsa05202:Transcriptional misregulation in cancer	5	3.36	0.372768	RXRB, RXRA, ELANE, MET, MMP3
hsa05166:HTLV-I infection	5	3.36	0.698634	HRAS, TGFBR1, GSK3B, LCK, AKT2
hsa05216:Thyroid cancer	4	2.68	0.015636	MAPK1, HRAS, RXRB, RXRA
hsa00500:Starch and sucrose metabolism	4	2.68	0.022142	GCK, PYGL, HK1, AMY2A
hsa04960:Aldosterone-regulated sodium reabsorption	4	2.68	0.034269	MAPK1, PDPK1, NR3C2, INSR
hsa00520:Amino sugar and nucleotide sugar metabolism	4	2.68	0.057649	UAP1, GCK, HK1, CHIT1
hsa05014:Amyotrophic lateral sclerosis (ALS)	4	2.68	0.063649	CASP3, MAPK14, RAB5A, CASP1
hsa00140:Steroid hormone biosynthesis	4	2.68	0.090339	AKR1C3, HSD17B1, HSD11B1, SULT2B1
hsa00590:Arachidonic acid metabolism	4	2.68	0.105171	AKR1C3, PLA2G2A, LTA4H, HPGDS
hsa05131:Shigellosis	4	2.68	0.112924	MAPK1, MAPK14, MAPK10, SRC
hsa05212:Pancreatic cancer	4	2.68	0.116881	MAPK1, TGFBR1, MAPK10, AKT2
hsa05211:Renal cell carcinoma	4	2.68	0.116881	MAPK1, HRAS, MET, AKT2
hsa00010:Glycolysis / Gluconeogenesis	4	2.68	0.124949	GCK, ADH5, HK1, PCK1
hsa04976:Bile secretion	4	2.68	0.133212	SULT2A1, HMGCR, RXRA, CA2
hsa05220:Chronic myeloid	4	2.68	0.145953	MAPK1, HRAS, TGFBR1, AKT2

leukemia					
hsa05132:Salmonella infection	4	2.68	0.195681	MAPK1, MAPK14, MAPK10, CASP1	
hsa05323:Rheumatoid arthritis	4	2.68	0.219527	CTSK, TEK, MMP3, MMP1	
hsa04750:Inflammatory mediator regulation of TRP channels	4	2.68	0.268759	MAPK14, MAPK10, PPP1CC, SRC	
hsa04725:Cholinergic synapse	4	2.68	0.334308	MAPK1, HRAS, JAK2, AKT2	
hsa04261:Adrenergic signaling in cardiomyocytes	4	2.68	0.505614	MAPK1, MAPK14, PPP1CC, AKT2	
hsa04145:Phagosome	4	2.68	0.537327	CD209, TAP1, RAB5A, EEA1	
hsa04921:Oxytocin signaling pathway	4	2.68	0.55927	MAPK1, HRAS, PPP1CC, SRC	
hsa05034:Alcoholism	4	2.68	0.636754	MAPK1, HRAS, PPP1CC, PKIA	
hsa04080:Neuroactive ligand-receptor interaction	4	2.68	0.890019	THRA, THRB, F2, NR3C1	
hsa05206:MicroRNAs in cancer	4	2.68	0.901048	CASP3, HRAS, MET, PIM1	
hsa00670:One carbon pool by folate	3	2.01	0.051325	TYMS, DHFR, GART	
hsa00760:Nicotinate and nicotinamide metabolism	3	2.01	0.098673	NT5M, BST1, NMNAT1	
hsa00052:Galactose metabolism	3	2.01	0.104497	GCK, AKR1B1, HK1	
hsa00051:Fructose and mannose metabolism	3	2.01	0.116413	SORD, AKR1B1, HK1	
hsa05340:Primary immunodeficiency	3	2.01	0.128653	LCK, TAP1, ZAP70	
hsa00270:Cysteine and methionine metabolism	3	2.01	0.153952	BHMT, MTAP, AMD1	

hsa04973:Carbohydrate digestion and absorption	3	2.01	0.18011	HK1, AMY2A, AKT2
hsa04913:Ovarian steroidogenesis	3	2.01	0.227222	AKR1C3, HSD17B1, INSR
hsa04150:mTOR signaling pathway	3	2.01	0.288789	MAPK1, PDPK1, AKT2
hsa05214:Glioma	3	2.01	0.336387	MAPK1, HRAS, AKT2
hsa04720:Long-term potentiation	3	2.01	0.343121	MAPK1, HRAS, PPP1CC
hsa05140:Leishmaniasis	3	2.01	0.376444	MAPK1, MAPK14, JAK2
hsa04612:Antigen processing and presentation	3	2.01	0.409067	HSP90AB1, HSP90AA1, TAP1
hsa04666:Fc gamma R-mediated phagocytosis	3	2.01	0.459475	MAPK1, AKT2, SYK
hsa04064:NF-kappa B signaling pathway	3	2.01	0.477738	LCK, ZAP70, SYK
hsa04974:Protein digestion and absorption	3	2.01	0.483743	MME, PGA4, DPP4
hsa04540:Gap junction	3	2.01	0.483743	MAPK1, HRAS, SRC
hsa04972:Pancreatic secretion	3	2.01	0.513124	BST1, PLA2G2A, CA2
hsa04916:Melanogenesis	3	2.01	0.552388	MAPK1, HRAS, GSK3B
hsa04723:Retrograde endocannabinoid signalling	3	2.01	0.557814	MAPK1, MAPK14, MAPK10
hsa04726:Serotonergic synapse	3	2.01	0.609509	MAPK1, CASP3, HRAS
hsa01200:Carbon metabolism	3	2.01	0.619285	GCK, ADH5, HK1
hsa04270:Vascular smooth muscle contraction	3	2.01	0.647493	MAPK1, PLA2G2A, PPP1CC
hsa04110:Cell cycle	3	2.01	0.669727	GSK3B, CCNA2, CDK2

hsa04530:Tight junction	3	2.01	0.722283	HRAS, SRC, AKT2
hsa04310:Wnt signaling pathway	3	2.01	0.726021	PPARD, GSK3B, MAPK10
hsa04630:Jak-STAT signaling pathway	3	2.01	0.751023	PIM1, JAK2, AKT2
hsa04390:Hippo signaling pathway	3	2.01	0.770881	TGFBR1, GSK3B, PPP1CC
hsa04141:Protein processing in endoplasmic reticulum	3	2.01	0.822438	HSP90AB1, HSP90AA1, MAPK10
hsa04060:Cytokine-cytokine receptor interaction	3	2.01	0.928828	TGFBR1, MET, KDR

REFERENCE

1. Jing, W.; Chunhua, M.; Shumin, W., Effects of acteoside on lipopolysaccharide-induced inflammation in acute lung injury via regulation of NF-kappaB pathway in vivo and in vitro. *Toxicology and applied pharmacology* **2015**, *285* (2), 128-35.
2. Lee, J. Y.; Woo, E. R.; Kang, K. W., Inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by acteoside through blocking of AP-1 activation. *Journal of ethnopharmacology* **2005**, *97* (3), 561-6.
3. Peng, X. M.; Gao, L.; Huo, S. X.; Liu, X. M.; Yan, M., The Mechanism of Memory Enhancement of Acteoside (Verbascoside) in the Senescent Mouse Model Induced by a Combination of D-gal and AlCl₃. *Phytotherapy research : PTR* **2015**, *29* (8), 1137-44.
4. Hong, S.; Oh, G. W.; Kang, W. G.; Kim, O., Anticoccidial effects of the *Plantago asiatica* extract on experimental *Eimeria tenella* infection. *Laboratory animal research* **2016**, *32* (1), 65-9.
5. Ravn, H.; Nishibe, S.; Sasahara, M.; Li, X. B., Phenolic-Compounds From *Plantago-Asiatica*. *Phytochemistry* **1990**, *29* (11), 3627-3631.
6. Koo, K. A.; Kim, S. H.; Oh, T. H.; Kim, Y. C., Acteoside and its aglycones protect primary cultures of rat cortical cells from glutamate-induced excitotoxicity. *Life sciences* **2006**, *79* (7), 709-16.
7. Li, H. M.; Kim, J. K.; Jang, J. M.; Cui, C. B.; Lim, S. S., Analysis of the inhibitory activity of *Abeliophyllum distichum* leaf constituents against aldose reductase by using high-speed counter current chromatography. *Archives of pharmacal research* **2013**, *36* (9), 1104-12.
8. Yu, S. Y.; Lee, I. S.; Jung, S. H.; Lee, Y. M.; Lee, Y. R.; Kim, J. H.; Sun, H.; Kim, J. S., Caffeoylated phenylpropanoid glycosides from *Brandisia hancei* inhibit advanced glycation end product formation and aldose reductase in vitro and vessel dilation in larval zebrafish in vivo. *Planta medica* **2013**, *79* (18), 1705-9.
9. Lines, T. C.; Ono, M., FRS 1000, an extract of red onion peel, strongly inhibits phosphodiesterase 5A (PDE 5A). *Phytomedicine : international journal of phytotherapy and phytopharmacology* **2006**, *13* (4), 236-9.
10. Fridrich, D.; Teller, N.; Esselen, M.; Pahlke, G.; Marko, D., Comparison of delphinidin, quercetin and (-)-epigallocatechin-3-gallate as inhibitors of the EGFR and the ErbB2 receptor phosphorylation. *Molecular nutrition & food research* **2008**, *52* (7), 815-22.
11. Davies, S. P.; Reddy, H.; Caivano, M.; Cohen, P., Specificity and mechanism of action of some commonly used protein kinase inhibitors. *Biochem J* **2000**, *351*, 95-105.
12. Escande, C.; Nin, V.; Price, N. L.; Capellini, V.; Gomes, A. P.; Barbosa, M. T.; O'Neil, L.; White, T. A.; Sinclair, D. A.; Chini, E. N., Flavonoid Apigenin Is an Inhibitor of the NAD(+)ase CD38: Implications for Cellular NAD(+) Metabolism, Protein Acetylation, and Treatment of Metabolic Syndrome (vol 62, pg 1084, 2013). *Diabetes* **2014**, *63* (4), 1428-1428.
13. Kang, T. B.; Liang, N. C., Effect of quercetin on activities of protein kinase C and tyrosine protein kinase from HL-60 cells. *Acta Pharmacol Sin* **1997**, *18* (4), 374-376.
14. Chan, A. L. F.; Huang, H. L.; Chien, H. C.; Chen, C. M.; Lin, C. N.; Ko, W. C., Inhibitory effects of quercetin derivatives on phosphodiesterase isozymes and high-affinity [H-3]-rolipram binding in guinea pig tissues. *Invest New Drug* **2008**, *26* (5), 417-424.
15. Baron, B. W.; Thirman, M. J.; Giurcanu, M. C.; Baron, J. M., Quercetin Therapy for Selected Patients with PIM1 Kinase-Positive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Pilot Study. *Acta Haematol-Basel* **2018**, *139* (2), 132-139.
16. van der Woude, H.; ter Veld, M. G. R.; Jacobs, N.; van der Saag, P. T.; Murk, A. J.; Rietjens, I. M. C.

M., The stimulation of cell proliferation by quercetin is mediated by the estrogen receptor. *Molecular nutrition & food research* **2005**, *49* (8), 763-771.

17. Lee, J. H.; Chung, K. Y.; Bang, D.; Lee, K. H., Searching for aging-related proteins in human dermal microvascular endothelial cells treated with anti-aging agents. *Proteomics* **2006**, *6* (4), 1351-1361.

18. Boly, R.; Gras, T.; Lamkami, T.; Guissou, P.; Serteyn, D.; Kiss, R.; Dubois, J., Quercetin inhibits a large panel of kinases implicated in cancer cell biology. *Int J Oncol* **2011**, *38* (3), 833-842.

19. Liu, Y.; Zhao, B.; Mao, G.; Fang, X.; Liu, Y.; Huang, Y.; Wang, N., Epigallocatechin-3-O-gallate, a green tea polyphenol, induces expression of pim-1 kinase via PPARgamma in human vascular endothelial cells. *Cardiovascular toxicology* **2013**, *13* (4), 391-5.

20. Lee, J. W.; Lee, Y. K.; Ban, J. O.; Ha, T. Y.; Yun, Y. P.; Han, S. B.; Oh, K. W.; Hong, J. T., Green Tea (-)-Epigallocatechin-3-Gallate Inhibits beta-Amyloid-Induced Cognitive Dysfunction through Modification of Secretase Activity via Inhibition of ERK and NF-kappa B Pathways in Mice. *J Nutr* **2009**, *139* (10), 1987-1993.

21. Landis-Piwowar, K.; Chen, D.; Chan, T. H.; Dou, Q. P., Inhibition of catechol-O-methyltransferase activity in human breast cancer cells enhances the biological effect of the green tea polyphenol (-)-EGCG. *Oncol Rep* **2010**, *24* (2), 563-569.

22. Lee, W. J.; Shim, J. Y.; Zhu, B. T., Mechanisms for the inhibition of DNA methyltransferases by tea catechins and bioflavonoids. *Molecular pharmacology* **2005**, *68* (4), 1018-1030.

23. Zheng, R.; Chen, T. S.; Lu, T., A comparative reverse docking strategy to identify potential antineoplastic targets of tea functional components and binding mode. *Int J Mol Sci* **2011**, *12* (8), 5200-12.

24. Chen, W. C.; Hsieh, S. R.; Chiu, C. H.; Hsu, B. D.; Liou, Y. M., Molecular identification for epigallocatechin-3-gallate-mediated antioxidant intervention on the H₂O₂-induced oxidative stress in H9c2 rat cardiomyoblasts. *Journal of biomedical science* **2014**, *21*, 56.

25. Lee, K., Transactivation of peroxisome proliferator-activated receptor alpha by green tea extracts. *Journal of veterinary science* **2004**, *5* (4), 325-30.

26. Ahmed, S.; Wang, N. Z.; Lalonde, M.; Goldberg, V. M.; Haqqi, T. M., Green tea polyphenol epigallocatechin-3-gallate (EGCG) differentially inhibits interleukin-1 beta-induced expression of matrix metalloproteinase-1 and-13 in human chondrocytes. *J Pharmacol Exp Ther* **2004**, *308* (2), 767-773.

27. Chow, H. H. S.; Hakim, I. A.; Vining, D. R.; Crowell, J. A.; Tome, M. E.; Ranger-Moore, J.; Cordova, C. A.; Mikhael, D. M.; Briehl, M. M.; Alberts, D. S., Modulation of human glutathione S-transferases by Polyphenon E intervention. *Cancer Epidem Biomar* **2007**, *16* (8), 1662-1666.