

Supporting Information

Title: Interpreting the pharmacological mechanisms of Sho-saiko-to on thyroid carcinoma through combining network pharmacology and experimental evaluation

Authors:

Kun Wang^{1,2}, Ruijie Qian^{1,2}, Hongyan Li^{1,2}, Chenyang Wang^{1,2}, Ying Ding^{1,2}, Zairong Gao^{1,2*}

Affiliations:

¹ Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

² Hubei Key Laboratory of Molecular Imaging, Wuhan 430022, China

Corresponding author:

Zairong Gao, MD, Ph.D.

Address:

Department of Nuclear Medicine, Union Hospital, Tongji Medical College,
Huazhong University of Science and Technology, Wuhan 430022, China
Hubei Key Laboratory of Molecular Imaging, Wuhan 430022, China

Tel.: +86-13986151287 (mobile)

E-mail: gaobonn@163.com

Funding: This work was supported by the National Natural Science Foundation of China (No. 81771866) and opening foundation of Hubei key laboratory of molecular imaging (2020fzyx023).

Table S1. The active ingredients of Sho-saiko-to

Herbs	Mol ID	Molecule Name	OB (%)	DL
banxia	MOL000358	beta-sitosterol	36.91	0.75
banxia	MOL000519	coniferin	31.11	0.32
banxia	MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76
banxia	MOL002670	Cavidine	35.64	0.81
banxia	MOL002714	baicalein	33.52	0.21
banxia	MOL003578	Cycloartenol	38.69	0.78
banxia	MOL005030	gondoic acid	30.7	0.2
banxia	MOL006936	10,13-eicosadienoic	39.99	0.2
banxia	MOL006937	12,13-epoxy-9-hydroxynonadeca-7,10-di enoic acid	42.15	0.24
banxia	MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)p iperazine-2,5-quinone	46.89	0.27
banxia	MOL006967	beta-D-Ribofuranoside, xanthine-9	44.72	0.21
chaihu	MOL000098	quercetin	46.43	0.28
chaihu	MOL000354	isorhamnetin	49.6	0.31
chaihu	MOL000422	kaempferol	41.88	0.24
chaihu	MOL000449	Stigmasterol	43.83	0.76
chaihu	MOL000490	petunidin	30.05	0.31
chaihu	MOL001645	Linoleyl acetate	42.1	0.2
chaihu	MOL002776	Baicalin	40.12	0.75
chaihu	MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxy phenyl)chromone	31.97	0.59
chaihu	MOL004609	Areapillin	48.96	0.41
chaihu	MOL004624	Longikaurin A	47.72	0.53
chaihu	MOL004628	Octalupine	47.82	0.28
chaihu	MOL004644	Sainfuran	79.91	0.23
chaihu	MOL004648	Troxeutin	31.6	0.28
chaihu	MOL004653	(+)-Anomalin	46.06	0.66
chaihu	MOL004702	saikosaponin c_qt	30.5	0.63
chaihu	MOL004718	α -spinasterol	42.98	0.76
chaihu	MOL013187	Cubebin	57.13	0.64
dazao	MOL000096	(-)-catechin	49.68	0.24
dazao	MOL000211	Mairin	55.38	0.78
dazao	MOL000492	(+)-catechin	54.83	0.24
dazao	MOL000627	Stepholidine	33.11	0.54
dazao	MOL000783	Protoporphyrin	30.86	0.56
dazao	MOL001454	berberine	36.86	0.78
dazao	MOL001522	(S)-Coclaurine	42.35	0.24

dazao	MOL002773	beta-carotene	37.18	0.58
dazao	MOL003410	Ziziphin_qt	66.95	0.62
dazao	MOL004350	Ruvoside_qt	36.12	0.76
dazao	MOL007213	Nuciferin	34.43	0.4
dazao	MOL008034	21302-79-4	73.52	0.77
dazao	MOL008647	Moupinamide	86.71	0.26
dazao	MOL012921	stepharine	31.55	0.33
dazao	MOL012940	Spiradine A	113.52	0.61
dazao	MOL012946	zizyphus saponin I_qt	32.69	0.62
dazao	MOL012961	jujuboside A_qt	36.67	0.62
dazao	MOL012976	coumestrol	32.49	0.34
dazao	MOL012980	Daechuine S6	46.48	0.79
dazao	MOL012981	Daechuine S7	44.82	0.83
dazao	MOL012986	Jujubasaponin V_qt	36.99	0.63
dazao	MOL012989	Jujuboside C_qt	40.26	0.62
dazao	MOL012992	Mauritine D	89.13	0.45
dazao	MOL013357	(3S,6R,8S,9S,10R,13R,14S,17R)-17-[(1R,4R)-4-ethyl-1,5-dimethylhexyl]-10,13-dimethyl-2,3,6,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3,6-diol	34.37	0.78
gancao	MOL000239	Jaranol	50.83	0.29
gancao	MOL000392	formononetin	69.67	0.21
gancao	MOL000417	Calycosin	47.75	0.24
gancao	MOL000497	licochalcone a	40.79	0.29
gancao	MOL000500	Vestitol	74.66	0.21
gancao	MOL001484	Inermine	75.18	0.54
gancao	MOL001792	DFV	32.76	0.18
gancao	MOL002311	Glycyrol	90.78	0.67
gancao	MOL002565	Medicarpin	49.22	0.34
gancao	MOL003656	Lupiwighteone	51.64	0.37
gancao	MOL003896	7-Methoxy-2-methyl isoflavone	42.56	0.2
gancao	MOL004328	naringenin	59.29	0.21
gancao	MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihdropyrano[2,3-f]chromen-4-one	31.79	0.72
gancao	MOL004806	euchrenone	30.29	0.57
gancao	MOL004808	glyasperin B	65.22	0.44
gancao	MOL004810	glyasperin F	75.84	0.54
gancao	MOL004811	Glyasperin C	45.56	0.4
gancao	MOL004814	Isotrifoliol	31.94	0.42

gancao	MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one	39.62	0.35
gancao	MOL004820	kanzonols W	50.48	0.52
gancao	MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofur[3,2-g]chromen-7-one	60.25	0.63
gancao	MOL004827	Semilicoisoflavone B	48.78	0.55
gancao	MOL004828	Glepidotin A	44.72	0.35
gancao	MOL004829	Glepidotin B	64.46	0.34
gancao	MOL004833	Phaseolinisoflavan	32.01	0.45
gancao	MOL004835	Glypallichalcone	61.6	0.19
gancao	MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	58.44	0.38
gancao	MOL004841	Licochalcone B	76.76	0.19
gancao	MOL004848	licochalcone G	49.25	0.32
gancao	MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	59.62	0.43
gancao	MOL004855	Licoricone	63.58	0.47
gancao	MOL004856	Gancaonin A	51.08	0.4
gancao	MOL004857	Gancaonin B	48.79	0.45
gancao	MOL004860	licorice glycoside E	32.89	0.27
gancao	MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone	66.37	0.41
gancao	MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	30.49	0.41
gancao	MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone	44.15	0.41
gancao	MOL004879	Glycyrin	52.61	0.47
gancao	MOL004882	Licocoumarone	33.21	0.36
gancao	MOL004883	Licoisoflavone	41.61	0.42
gancao	MOL004884	Licoisoflavone B	38.93	0.55
gancao	MOL004885	licoisoflavanone	52.47	0.54
gancao	MOL004891	shinpterocarpin	80.3	0.73
gancao	MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one	46.27	0.31
gancao	MOL004903	liquiritin	65.69	0.74
gancao	MOL004904	licopyranocoumarin	80.36	0.65
gancao	MOL004905	3,22-Dihydroxy-11-oxo-delta(12)-oleane-27-alpha-methoxycarbonyl-29-oic	34.32	0.55

		acid		
gancao	MOL004907	Glyzaglabrin	61.07	0.35
gancao	MOL004908	Glabridin	53.25	0.47
gancao	MOL004910	Glabranin	52.9	0.31
gancao	MOL004911	Glabrene	46.27	0.44
gancao	MOL004912	Glabrone	52.51	0.5
gancao	MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano [3,2-c]chromenone	48.14	0.43
gancao	MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofur ano[3,2-c]chromenone	62.9	0.53
gancao	MOL004915	Eurycarpin A	43.28	0.37
gancao	MOL004917	glycyroside	37.25	0.79
gancao	MOL004924	(-)-Medicocarpin	40.99	0.95
gancao	MOL004935	Sigmoidin-B	34.88	0.41
gancao	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chr oman-4-one	71.12	0.18
gancao	MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	36.57	0.32
gancao	MOL004948	Isoglycyrol	44.7	0.84
gancao	MOL004949	Isolicoflavonol	45.17	0.42
gancao	MOL004957	HMO	38.37	0.21
gancao	MOL004959	1-Methoxyphaseollidin	69.98	0.64
gancao	MOL004961	Quercetin der.	46.45	0.33
gancao	MOL004966	3'-Hydroxy-4'-O-Methylglabridin	43.71	0.57
gancao	MOL004974	3'-Methoxyglabridin	46.16	0.57
gancao	MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyr ano[6,5-f]chromen-3-yl]-5-methoxyphen ol	36.21	0.52
gancao	MOL004980	Inflacoumarin A	39.71	0.33
gancao	MOL004985	icos-5-enoic acid	30.7	0.2
gancao	MOL004988	Kanzonol F	32.47	0.89
gancao	MOL004989	6-prenylated eriodictyol	39.22	0.41
gancao	MOL004990	7,2',4'-trihydroxy-5-methoxy-3- arylcoumarin	83.71	0.27
gancao	MOL004991	7-Acetoxy-2-methylisoflavone	38.92	0.26
gancao	MOL004993	8-prenylated eriodictyol	53.79	0.4
gancao	MOL004996	gadelaidic acid	30.7	0.2
gancao	MOL005000	Gancaonin G	60.44	0.39
gancao	MOL005001	Gancaonin H	50.1	0.78
gancao	MOL005003	Licoagrocarpin	58.81	0.58
gancao	MOL005007	Glyasperins M	72.67	0.59

gancao	MOL005008	Glycyrrhiza flavonol A	41.28	0.6
gancao	MOL005012	Licoagroisoflavone	57.28	0.49
gancao	MOL005013	18 α -hydroxyglycyrrhetic acid	41.16	0.71
gancao	MOL005016	Odoratin	49.95	0.3
gancao	MOL005017	Phaseol	78.77	0.58
gancao	MOL005018	Xambioona	54.85	0.87
gancao	MOL005020	dehydroglyasperins C	53.82	0.37
huangqin	MOL000073	ent-Epicatechin	48.96	0.24
huangqin	MOL000173	wogonin	30.68	0.23
huangqin	MOL000228	(2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one	55.23	0.2
huangqin	MOL000359	sitosterol	36.91	0.75
huangqin	MOL000525	Norwogonin	39.4	0.21
huangqin	MOL000552	5,2'-Dihydroxy-6,7,8-trimethoxyflavone	31.71	0.35
huangqin	MOL001458	coptisine	30.67	0.86
huangqin	MOL001490	bis[(2S)-2-ethylhexyl]benzene-1,2-dicarboxylate	43.59	0.35
huangqin	MOL001506	Supraene	33.55	0.42
huangqin	MOL001689	acacetin	34.97	0.24
huangqin	MOL002897	epiberberine	43.09	0.78
huangqin	MOL002908	5,8,2'-Trihydroxy-7-methoxyflavone	37.01	0.27
huangqin	MOL002909	5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone	33.82	0.45
huangqin	MOL002910	Carthamidin	41.15	0.24
huangqin	MOL002911	2,6,2',4'-tetrahydroxy-6'-methoxychalcone	69.04	0.22
huangqin	MOL002913	Dihydrobaicalin_qt	40.04	0.21
huangqin	MOL002914	Eriodyctiol (flavanone)	41.35	0.24
huangqin	MOL002915	Salvigenin	49.07	0.33
huangqin	MOL002917	5,2',6'-Trihydroxy-7,8-dimethoxyflavone	45.05	0.33
huangqin	MOL002925	5,7,2',6'-Tetrahydroxyflavone	37.01	0.24
huangqin	MOL002926	dihydrooroxylin A	38.72	0.23
huangqin	MOL002927	Skullcapflavone II	69.51	0.44
huangqin	MOL002928	oroxylin a	41.37	0.23
huangqin	MOL002932	Panicolin	76.26	0.29
huangqin	MOL002933	5,7,4'-Trihydroxy-8-methoxyflavone	36.56	0.27
huangqin	MOL002934	NEOBAICALEIN	104.34	0.44
huangqin	MOL002937	DIHYDROOROXYLIN	66.06	0.23
huangqin	MOL008206	Moslosooflavone	44.09	0.25
huangqin	MOL010415	11,13-Eicosadienoic acid, methyl ester	39.28	0.23
huangqin	MOL012245	5,7,4'-trihydroxy-6-methoxyflavanone	36.63	0.27

huangqin	MOL012246	5,7,4'-trihydroxy-8-methoxyflavanone	74.24	0.26
huangqin	MOL012266	rivularin	37.94	0.37
renshen	MOL000787	Fumarine	59.26	0.83
renshen	MOL002879	Diop	43.59	0.39
renshen	MOL003648	Inermin	65.83	0.54
renshen	MOL004492	Chrysanthemaxanthin	38.72	0.58
renshen	MOL005308	Aposiopoline	66.65	0.22
renshen	MOL005314	Celabenzine	101.88	0.49
renshen	MOL005317	Deoxyharringtonine	39.27	0.81
renshen	MOL005318	Dianthramine	40.45	0.2
renshen	MOL005320	arachidonate	45.57	0.2
renshen	MOL005321	Frutinone A	65.9	0.34
renshen	MOL005344	ginsenoside rh2	36.32	0.56
renshen	MOL005348	Ginsenoside-Rh4_qt	31.11	0.78
renshen	MOL005356	Girinimbin	61.22	0.31
renshen	MOL005357	Gomisin B	31.99	0.83
renshen	MOL005360	malkangunin	57.71	0.63
renshen	MOL005376	Panaxadiol	33.09	0.79
renshen	MOL005384	suchilactone	57.52	0.56
renshen	MOL005399	alexandrin_qt	36.91	0.75
renshen	MOL005401	ginsenoside Rg5_qt	39.56	0.79
shengjiang	MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
shengjiang	MOL006129	6-methylgingediacetate2	48.73	0.32
shengjiang	MOL008698	Dihydrocapsaicin	47.07	0.19

Table S2. The targets genes of Sho-saiko-to

Mol ID	Molecule name	Target name	Target gene
MOL000422	kaempferol	Vascular cell adhesion protein 1	ABAT
MOL000449	Stigmasterol	Urokinase-type plasminogen activator	ABCA2
MOL000422	kaempferol	Type I iodothyronine deiodinase	ABCC1
MOL000422	kaempferol	Tumor necrosis factor	ACACA
MOL002714	baicalein	Trypsin-1	ACHE
MOL000358	beta-sitosterol	Transforming growth factor beta-1	ACP3
MOL002714	baicalein	Transcription factor p65	ADCYAP1
MOL000098	quercetin	Transcription factor E2F2	ADH1C
MOL000098	quercetin	Transcription factor E2F1	ADIPOQ
MOL000358	beta-sitosterol	Transcription factor AP-1	ADRA1A
MOL000098	quercetin	Tissue-type plasminogen activator	ADRA1B
MOL000098	quercetin	Tissue factor	ADRA1D
MOL000098	quercetin	Thrombomodulin	ADRA2A
MOL000422	kaempferol	Thrombin	ADRA2B
MOL000098	quercetin	Superoxide dismutase [Cu-Zn]	ADRA2C
MOL000098	quercetin	Stromelysin-1	ADRB1
MOL000422	kaempferol	Solute carrier family 2, facilitated glucose transporter member 4	ADRB2
MOL000449	Stigmasterol	Sodium-dependent noradrenaline transporter	AHR
MOL000449	Stigmasterol	Sodium-dependent dopamine transporter	AHSA1
MOL000449	Stigmasterol	Sodium channel protein type 5 subunit alpha	AKR1C1
MOL000422	kaempferol	Signal transducer and activator of transcription 1-alpha/beta	AKR1C3
MOL000358	beta-sitosterol	Serum paraoxonase/arylesterase 1	AKT1
MOL000422	kaempferol	Serine/threonine-protein phosphatase 2B catalytic subunit alpha isoform	ALB
MOL000098	quercetin	Serine/threonine-protein kinase Chk2	APOB
MOL000173	wogonin	Serine/threonine-protein kinase Chk1	APOD
MOL000098	quercetin	Runt-related transcription factor 2	AR
MOL002670	Cavidine	Retinoic acid receptor RXR-alpha	ATP5F1B
MOL000098	quercetin	Retinoblastoma-associated protein	BAD
MOL000098	quercetin	Receptor tyrosine-protein kinase erbB-3	BAX
MOL000098	quercetin	Receptor tyrosine-protein kinase erbB-2	BCL2
MOL000098	quercetin	Ras GTPase-activating protein 1	BCL2L1

MOL000098	quercetin	Ras association domain-containing protein 1	BIRC5
MOL000098	quercetin	RAF proto-oncogene serine/threonine-protein kinase	CA2
MOL002714	baicalein	RAC-alpha serine/threonine-protein kinase	CACNA1S
MOL000098	quercetin	Puromycin-sensitive aminopeptidase 1	CACNA2D
MOL000392	formononetin	Proto-oncogene serine/threonine-protein kinase Pim-1	CASP1
MOL002714	baicalein	Proto-oncogene c-Fos	CASP3
MOL000098	quercetin	Protein kinase C beta type	CASP7
MOL000358	beta-sitosterol	Protein kinase C alpha type	CASP8
MOL000098	quercetin	Protein CBFA2T1	CASP9
MOL000098	quercetin	Prostatic acid phosphatase	CAT
MOL006967	beta-D-Ribofuran oside, xanthine-9	Prostaglandin G/H synthase 2	CAV1
MOL006936	10,13-eicosadieno ic	Prostaglandin G/H synthase 1	CCL2
MOL000173	wogonin	Prostaglandin E2 receptor EP3 subtype	CCNA2
MOL001755	24-Ethylcholest-4 -en-3-one	Progesterone receptor	CCNB1
MOL000098	quercetin	Pro-epidermal growth factor	CCND1
MOL000098	quercetin	Procollagen C-endopeptidase enhancer 1	CD40LG
MOL000098	quercetin	Probable E3 ubiquitin-protein ligase HERC5	CDC37
MOL002670	Cavidine	Potassium voltage-gated channel subfamily H member 2	CDKN1A
MOL000098	quercetin	Poly [ADP-ribose] polymerase 1	CES1
MOL000098	quercetin	Plasminogen activator inhibitor 1	CHEK1
MOL002714	baicalein	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit, gamma isoform	CHEK2
MOL000098	quercetin	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	CHRM1
MOL000098	quercetin	Peroxisome proliferator-activated receptor alpha	CHRM2
MOL000422	kaempferol	Peroxisome proliferator activated receptor gamma	CHRM3
MOL000552	5,2'-Dihydroxy-6, 7,8-trimethoxyfla vone	Peroxisome proliferator activated receptor delta	CHRM4

MOL000422	kaempferol	Peroxidase C1A	CHRM5
MOL000354	isorhamnetin	Oxidized low-density lipoprotein receptor 1	CHRNA2
MOL000098	quercetin	Osteopontin	CHRNA7
MOL000098	quercetin	Ornithine decarboxylase	CHUK
MOL000422	kaempferol	Nuclear receptor subfamily 1 group I member 3	CLDN4
MOL000422	kaempferol	Nuclear receptor subfamily 1 group I member 2	COL1A1
MOL006936	10,13-eicosadienoic	Nuclear receptor coactivator 2	COL3A1
MOL002714	baicalein	Nuclear receptor coactivator 1	CRP
MOL000098	quercetin	Nuclear factor erythroid 2-related factor 2	CTNNB1
MOL000422	kaempferol	Nitric-oxide synthase, endothelial	CTRB1
MOL000422	kaempferol	Nitric oxide synthase, inducible	CTSD
MOL000098	quercetin	Nitric oxide synthase, endothelial	CXCL10
MOL005344	ginsenoside rh2	NF-kappa-B inhibitor alpha	CXCL11
MOL000098	quercetin	Neutrophil cytosol factor 1	CXCL2
MOL000449	Stigmasterol	Neuronal acetylcholine receptor protein, alpha-7 chain	CXCL8
MOL000098	quercetin	NADPH--cytochrome P450 reductase	CYCS
MOL000098	quercetin	NAD(P)H dehydrogenase [quinone] 1	CYP1A1
MOL002714	baicalein	Myeloperoxidase	CYP1A2
MOL000098	quercetin	Myc proto-oncogene protein	CYP1B1
MOL000449	Stigmasterol	Muscarinic acetylcholine receptor M3	CYP2B6
MOL000449	Stigmasterol	Muscarinic acetylcholine receptor M2	CYP2C9
MOL002670	Cavidine	Muscarinic acetylcholine receptor M1	CYP3A4
MOL002776	Baicalin	mRNA of Protein-tyrosine phosphatase, non-receptor type 1	DCAF5
MOL002714	baicalein	mRNA of PKA Catalytic Subunit C-alpha	DIO1
MOL000422	kaempferol	Mitogen-activated protein kinase 8	DPP4
MOL000173	wogonin	Mitogen-activated protein kinase 14	DRD2
MOL000098	quercetin	Mitogen-activated protein kinase 1	DRD4
MOL000449	Stigmasterol	Mineralocorticoid receptor	DRD5
MOL002714	baicalein	Matrix metalloproteinase-9	DUOX2
MOL000098	quercetin	Maltase-glucoamylase, intestinal	E2F1
MOL000449	Stigmasterol	Leukotriene A-4 hydrolase	E2F2
MOL000422	kaempferol	Interstitial collagenase	EGF
MOL000173	wogonin	Interleukin-8	EGFR
MOL000173	wogonin	Interleukin-6	EGLN1
MOL000098	quercetin	Interleukin-2	EIF6
MOL000098	quercetin	Interleukin-10	ELK1

MOL005344	ginsenoside rh2	Interleukin-1 beta	ERBB2
MOL000098	quercetin	Interleukin-1 alpha	ERBB3
MOL000098	quercetin	Interferon regulatory factor 1	ESR1
MOL005344	ginsenoside rh2	Interferon gamma	ESR2
MOL000422	kaempferol	Intercellular adhesion molecule 1	F3
MOL000098	quercetin	Insulin-like growth factor-binding protein 3	F7
MOL002714	baicalein	Insulin-like growth factor II	FABP5
MOL000422	kaempferol	Insulin receptor	FASLG
MOL000422	kaempferol	Inhibitor of nuclear factor kappa-B kinase subunit beta	FASN
MOL000098	quercetin	Inhibitor of nuclear factor kappa-B kinase subunit alpha	FN1
MOL000449	Stigmasterol	Ig gamma-1 chain C region	FOS
MOL002714	baicalein	Hypoxia-inducible factor 1-alpha	FOSL1
MOL000422	kaempferol	Hyaluronan synthase 2	FOSL2
MOL000098	quercetin	Homeobox protein Nkx-3.1	GABRA1
MOL000098	quercetin	Hexokinase-2	GABRA2
MOL000422	kaempferol	Heme oxygenase 1	GABRA3
MOL002714	baicalein	Heat shock protein HSP 90	GABRA5
MOL000098	quercetin	Heat shock protein beta-1	GABRA6
MOL000098	quercetin	Heat shock factor protein 1	GJA1
MOL000173	wogonin	Glycogen synthase kinase-3 beta	GOT1
MOL002909	5,7,2,5-tetrahydroxy-8,6-dimethoxy flavone	Glycogen phosphorylase, muscle form	GRIA2
MOL000422	kaempferol	Glutathione S-transferase P	GSK3B
MOL000422	kaempferol	Glutathione S-transferase Mu 2	GSR
MOL000422	kaempferol	Glutathione S-transferase Mu 1	GSTM1
MOL000354	isorhamnetin	Glutamate receptor 2	GSTM2
MOL000098	quercetin	Gap junction alpha-1 protein	GSTP1
MOL004624	Longikaurin A	Gamma-aminobutyric-acid receptor subunit alpha-6	gyrB
MOL000358	beta-sitosterol	Gamma-aminobutyric-acid receptor alpha-2 subunit	HAS2
MOL000449	Stigmasterol	Gamma-aminobutyric acid receptor subunit alpha-1	HEL-S-89n
MOL002714	baicalein	G2/mitotic-specific cyclin-B1	HIF1A
MOL000173	wogonin	G1/S-specific cyclin-D1	HK2
MOL000173	wogonin	Eukaryotic translation initiation factor 6	HMGCR
MOL000098	quercetin	ETS domain-containing protein Elk-1	HMOX1
MOL000098	quercetin	Estrogen sulfotransferase	HSD3B1

MOL000552	5,2'-Dihydroxy-6,7,8-trimethoxyflavone	Estrogen receptor beta	HSD3B2
MOL000073	ent-Epicatechin	Estrogen receptor	HSF1
MOL000422	kaempferol	E-selectin	HSP90AB1
MOL000098	quercetin	Epidermal growth factor receptor	HSPB1
MOL000098	quercetin	Dual oxidase 2	HTR2A
MOL002670	Cavidine	DNA topoisomerase II	HTR2C
MOL000098	quercetin	DNA topoisomerase 2-alpha	HTR3A
MOL000098	quercetin	DNA topoisomerase 1	ICAM1
MOL000098	quercetin	DNA gyrase subunit B	IFNG
MOL002714	baicalein	Dipeptidyl peptidase IV	IGF2
MOL000098	quercetin	DDB1- and CUL4-associated factor 5	IGFBP3
MOL000358	beta-sitosterol	Cytochrome P450-cam	IKBKB
MOL000422	kaempferol	Cytochrome P450 3A4	IL10
MOL000422	kaempferol	Cytochrome P450 1B1	IL1A
MOL000422	kaempferol	Cytochrome P450 1A2	IL1B
MOL000422	kaempferol	Cytochrome P450 1A1	IL2
MOL000098	quercetin	Cyclin-dependent kinase inhibitor 2A, isoforms 1/2/3	IL4
MOL000173	wogonin	Cyclin-dependent kinase inhibitor 1	IL6
MOL000392	formononetin	Cyclin-A2	INSR
MOL000098	quercetin	C-X-C motif chemokine 2	IRF1
MOL000098	quercetin	C-X-C motif chemokine 11	JUN
MOL000098	quercetin	C-X-C motif chemokine 10	JVH1_9171
MOL000098	quercetin	C-reactive protein	KCNH2
MOL000098	quercetin	Collagen alpha-1(III) chain	KCNMA1
MOL000098	quercetin	Collagen alpha-1(I) chain	KDR
MOL002670	Cavidine	Coagulation factor Xa	KLF7
MOL002670	Cavidine	Coagulation factor VII	LDLR
MOL000098	quercetin	Claudin-4	LTA4H
MOL000449	Stigmasterol	Chymotrypsinogen B	MAOA
MOL002714	baicalein	Cellular tumor antigen p53	MAOB
MOL000173	wogonin	Cell division protein kinase 2	MAP2
MOL002714	baicalein	Cell division control protein 2 homolog	MAP2K4
MOL000098	quercetin	CD40 ligand	MAPK1
MOL000173	wogonin	C-C motif chemokine 2	MAPK10
MOL000098	quercetin	Caveolin-1	MAPK14
MOL000098	quercetin	Cathepsin D	MAPK3
MOL000358	beta-sitosterol	Caspase-9	MAPK8

MOL000358	beta-sitosterol	Caspase-8	MCL1
MOL002714	baicalein	Caspase-3	MGAM
MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone	Calmodulin	MMP1
MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone	Beta-2 adrenergic receptor	MMP10
MOL002670	Cavidine	Beta-1 adrenergic receptor	MMP2
MOL000098	quercetin	Bcl-2-like protein 1	MMP3
MOL000098	quercetin	Baculoviral IAP repeat-containing protein 5	MMP9
MOL000098	quercetin	ATP-binding cassette sub-family G member 2	MPO
MOL002714	baicalein	Aryl hydrocarbon receptor	MT-ND6
MOL000422	kaempferol	Arachidonate 5-lipoxygenase	MTTP
MOL002714	baicalein	Apoptosis regulator Bcl-2	MYC
MOL002714	baicalein	Apoptosis regulator BAX	NCF1
MOL000422	kaempferol	Antileukoproteinase	NCOA1
MOL002714	baicalein	Androgen receptor	NCOA2
MOL000449	Stigmasterol	Amine oxidase [flavin-containing] B	NFATC1
MOL000449	Stigmasterol	Amine oxidase [flavin-containing] A	NFE2L2
MOL000449	Stigmasterol	Alpha-2A adrenergic receptor	NFKBIA
MOL000449	Stigmasterol	Alpha-1B adrenergic receptor	NKX3-1
MOL000449	Stigmasterol	Alpha-1A adrenergic receptor	NOS2
MOL000449	Stigmasterol	Aldose reductase	NOS3
MOL000449	Stigmasterol	Alcohol dehydrogenase 1C	NOX5
MOL000422	kaempferol	Activator of 90 kDa heat shock protein ATPase homolog 1	NPEPPS
MOL000098	quercetin	Acetyl-CoA carboxylase 1	NQO1
MOL000422	kaempferol	Acetylcholinesterase	NR1I2
MOL000098	quercetin	78 kDa glucose-regulated protein	NR1I3
MOL000098	quercetin	72 kDa type IV collagenase	NR3C1
MOL000449	Stigmasterol	5-hydroxytryptamine 2A receptor	NR3C2
MOL000422	kaempferol	26S proteasome non-ATPase regulatory subunit 3	ODC1
MOL002670	Cavidine	Dopamine D1 receptor	OLR1
MOL002670	Cavidine	Muscarinic acetylcholine receptor M4	OPRD1
MOL002714	baicalein	CGMP-inhibited 3',5'-cyclic phosphodiesterase A	OPRM1

MOL000358	beta-sitosterol	Gamma-aminobutyric-acid receptor alpha-5 subunit	PCOLCE
MOL000449	Stigmasterol	Gamma-aminobutyric-acid receptor alpha-3 subunit	PDE10A
MOL000358	beta-sitosterol	Neuronal acetylcholine receptor subunit alpha-2	PDE3A
MOL002670	Cavidine	Sodium-dependent serotonin transporter	PGR
MOL002670	Cavidine	Mu-type opioid receptor	PIK3CG
MOL000358	beta-sitosterol	Microtubule-associated protein 2	PIM1
MOL012245	5,7,4'-trihydroxy-6-methoxyflavone	Carbonic anhydrase II	PKIA
MOL002670	Cavidine	Alpha-1D adrenergic receptor	PLAT
MOL000073	ent-Epicatechin	Beta-lactamase	PLAU
MOL002670	Cavidine	Muscarinic acetylcholine receptor M5	PLB1
MOL002670	Cavidine	5-hydroxytryptamine receptor 3A	PNP
MOL002670	Cavidine	Alpha-2C adrenergic receptor	PON1
MOL002670	Cavidine	Delta-type opioid receptor	POR
MOL002670	Cavidine	5-hydroxytryptamine 2C receptor	PPARA
MOL002670	Cavidine	Retinoic acid receptor RXR-beta	PPARD
MOL002714	baicalein	Fos-related antigen 1	PPARG
MOL002714	baicalein	Cytochrome c	PPP3CA
MOL002714	baicalein	Arachidonate 12-lipoxygenase, 12S-type	PRKCA
MOL002714	baicalein	Nuclear factor of activated T-cells, cytoplasmic 1	PRKCB
MOL002714	baicalein	Tudor domain-containing protein 7	PRKCD
MOL002714	baicalein	Egl nine homolog 1	PRSS1
MOL002714	baicalein	NADPH oxidase 5	PSMD3
MOL002714	baicalein	Fatty acid-binding protein, epidermal	PSMG1
MOL002714	baicalein	Apolipoprotein D	PTEN
MOL006967	beta-D-Ribofuranoside, xanthine-9	Purine nucleoside phosphorylase	PTGER3
MOL006967	beta-D-Ribofuranoside, xanthine-9	Purine nucleoside phosphorylase deoD-type	PTGS1
MOL000422	kaempferol	Peroxisome proliferator-activated receptor gamma	PTGS2
MOL000787	Fumarine	Voltage-dependent L-type calcium channel subunit alpha-1S	PYGM
MOL000787	Fumarine	Type IV phosphodiesterase	RAF1
MOL000787	Fumarine	Vascular endothelial growth factor receptor 2	RASA1

MOL005320	arachidonate	Retinoic acid receptor RXR-gamma	RASSF1
MOL005344	ginsenoside rh2	Caspase-1	RB1
MOL005344	ginsenoside rh2	Pituitary adenylate cyclase-activating polypeptide	RELA
MOL005344	ginsenoside rh2	Proteasome assembly chaperone 1	RUNX1T1
MOL005344	ginsenoside rh2	Dual specificity mitogen-activated protein kinase kinase 4	RUNX2
MOL005376	Panaxadiol	Glucocorticoid receptor	RXRA
MOL005384	suchilactone	Calcium-activated potassium channel subunit alpha 1	RXRB
MOL000173	wogonin	Bcl-2-binding component 3	RXRG
MOL000173	wogonin	Telomerase protein component 1	SCN5A
MOL000173	wogonin	Protein kinase C delta type	SELE
MOL000173	wogonin	Fibronectin	SERPINE1
MOL000173	wogonin	Induced myeloid leukemia cell differentiation protein Mcl-1	SIRT1
MOL000228	(2R)-7-hydroxy-5-methoxy-2-phenyl chroman-4-one	cAMP-dependent protein kinase inhibitor alpha	SLC2A4
MOL001689	acacetin	Fatty acid synthase	SLC6A2
MOL001689	acacetin	Tumor necrosis factor ligand superfamily member 6	SLC6A3
MOL001689	acacetin	Cytochrome P450 19A1	SLC6A4
MOL002927	Skullcapflavone II	Voltage-dependent calcium channel subunit alpha-2/delta-1	SLPI
MOL002928	oroxylin a	Cell division protein kinase 7	SOAT1
MOL002928	oroxylin a	Cytochrome P450 2C9	SOAT2
MOL000096	(-)-catechin	Krueppel-like factor 7	SOD1
MOL000098	quercetin	Peroxisome proliferator-activated receptor delta	SPP1
MOL000492	(+)-catechin	Catalase	SREBF1
MOL000627	Stepholidine	D(1B) dopamine receptor	STAT1
MOL000627	Stepholidine	D(4) dopamine receptor	STAT3
MOL000627	Stepholidine	Alpha-2B adrenergic receptor	TDRD7
MOL002773	beta-carotene	Cytochrome P450 2B1	TEP1
MOL002773	beta-carotene	Serum albumin	TGFB1
MOL002773	beta-carotene	Catenin beta-1	THBD
MOL002773	beta-carotene	Caspase-7	TNF
MOL002773	beta-carotene	Stromelysin-2	TNKS
MOL007213	Nuciferin	D(2) dopamine receptor	TOP1
MOL012976	coumestrol	Cytochrome P450 2B6	TOP2A

MOL012976	coumestrol	Hsp90 co-chaperone Cdc37	TOP2B
MOL000392	formononetin	Interleukin-4	TP53
MOL000392	formononetin	NAD-dependent deacetylase sirtuin-1	UGT1A1
MOL000392	formononetin	ATP synthase subunit beta, mitochondrial	VCAM1
MOL000392	formononetin	NADH-ubiquinone oxidoreductase chain 6	VEGFA
MOL000392	formononetin	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2	XDH

Table S3 the data of topological parameters of a PPI network

GENE	AVERAGE	CLOSENESS	BETWEENNESS	DEGREE
AKT1	1.86330935	0.53667954	0.1248589	43
STAT3	1.91366906	0.52255639	0.09330697	42
JUN	1.85611511	0.53875969	0.0739288	41
MAPK1	1.89208633	0.52851711	0.06770797	40
MAPK3	1.89208633	0.52851711	0.04669032	40
TP53	1.94964029	0.51291513	0.06707017	38
TNF	2.02158273	0.49466192	0.04913837	34
RELA	2.02877698	0.4929078	0.02561478	32
IL6	2.15107914	0.46488294	0.03244457	29
MAPK14	2.01438849	0.49642857	0.03735975	29
MAPK8	2.03597122	0.49116608	0.02611041	29
FOS	1.98561151	0.50362319	0.03220694	27
EGFR	2.08633094	0.47931034	0.04186283	26
ESR1	2.03597122	0.49116608	0.0289982	23
VEGFA	2.07913669	0.48096886	0.02635101	23
NR3C1	2.09352518	0.47766323	0.04055656	22
RXRA	2.0647482	0.48432056	0.0084648	22
CTNNB1	2.16546763	0.46179402	0.01803009	22
MYC	2.07913669	0.48096886	0.05094223	22
NCOA1	2.21582734	0.4512987	0.0230927	20
EGF	2.30935252	0.43302181	0.053355	20
CCND1	2.11510791	0.47278912	3.38E-02	19
RB1	2.15827338	0.46333333	0.02555992	19
STAT1	2.25899281	0.44267516	0.01694972	18
PRKCA	2.23021583	0.4483871	0.01055886	18
NCOA2	2.20863309	0.45276873	0.00986732	17
BCL2	2.3381295	0.42769231	0.0179216	17
FN1	2.34532374	0.42638037	0.01332546	17
IL1B	2.3381295	0.42769231	0.0035245	17
CXCL8	2.4028777	0.41616766	0.0220869	17
IL2	2.20863309	0.45276873	0.01361029	16
AR	2.23021583	0.4483871	0.00359205	16
TGFB1	2.32374101	0.43034056	0.00559919	16
PRKCD	2.3381295	0.42769231	0.01077395	16
IL4	2.21582734	0.4512987	0.01064286	16
PPARG	2.33093525	0.42901235	5.71E-03	15
BCL2L1	2.32374101	0.43034056	2.05E-02	15
CASP3	2.35251799	0.42507645	0.01342932	15

CASP8	2.28776978	0.43710692	3.24E-03	15
NFKBIA	2.24460432	0.44551282	2.86E-02	15
PPARA	2.25179856	0.44408946	0.00713856	15
PRKCB	2.37410072	0.42121212	0.00503951	15
CDKN1A	2.38129496	0.41993958	0.01940564	14
ALB	2.4028777	0.41616766	0.00253505	14
CCL2	2.28057554	0.4384858	0.00974108	14
ERBB2	2.33093525	0.42901235	0.00404729	13
RXRG	2.11510791	0.47278912	0.00416908	12
RXRB	2.47482014	0.40406977	0.00188967	12
HIF1A	2.51798561	0.39714286	0.0076281	12
IGF2	2.56834532	0.38935574	6.83E-04	12
IL10	2.47482014	0.40406977	0.01400753	12
MMP9	2.37410072	0.42121212	0.00345164	12
IFNG	2.37410072	0.42121212	0.00345164	12
APOB	2.50359712	0.39942529	0.0186223	11
SIRT1	2.51079137	0.3982808	0.00204435	11
RAF1	2.30215827	0.434375	0.00717337	11
NOS2	2.35971223	0.42378049	0.00181933	11
BAD	2.3381295	0.42769231	0.00280618	11
NOS3	2.34532374	0.42638037	0.00138658	10
GSK3B	2.61151079	0.38292011	0.0019746	10
IGFBP3	2.43165468	0.4112426	0.00575008	10
RASA1	2.38129496	0.41993958	0.00327293	10
ICAM1	2.48920863	0.4017341	0.00272742	10
CYP1A1	2.76258993	0.36197917	0.00506874	9
CD40LG	2.45323741	0.40762463	0.00277811	9
CYCS	2.82733813	0.35368957	0.00234411	9
MAPK10	2.79136691	0.35824742	0.08538951	9
CCNA2	2.47482014	0.40406977	2.11E-04	9
MMP3	2.47482014	0.40406977	9.16E-04	9
IL1A	2.45323741	0.40762463	0.00950195	9
ADIPOQ	2.51798561	0.39714286	0.00270946	8
CAV1	2.44604317	0.40882353	0.00243163	8
IKBKB	2.94244604	0.3398533	0.00276674	8
SERPINE1	2.48201439	0.40289855	0.00209449	8
PGR	2.69064748	0.37165775	0.00332601	8
CCNB1	2.54676259	0.39265537	0.0024519	8
MMP2	2.4676259	0.40524781	6.77E-04	8
PTGS2	2.70503597	0.36968085	0.01516722	8
E2F1	2.69784173	0.37066667	5.98E-04	7

SPP1	2.79136691	0.35824742	0.00251203	7
BAX	2.66906475	0.37466307	0.00175582	7
HMOX1	2.52517986	0.3960114	2.21E-04	7
VCAM1	2.5323741	0.39488636	8.96E-04	7
CXCL10	2.61151079	0.38292011	0.01802277	7
ELK1	2.61151079	0.38292011	8.12E-04	7
ESR2	2.72661871	0.36675462	0.00235551	7
IRF1	2.74820144	0.36387435	0.0017625	7
MMP1	2.67625899	0.37365591	0.00114884	7
CAT	2.6618705	0.37567568	0.00794077	6
HSPB1	2.69064748	0.37165775	0.01657211	6
PTEN	2.47482014	0.40406977	0.00231909	6
MCL1	2.60431655	0.3839779	4.54E-04	6
BIRC5	2.64028777	0.37874659	0.01336038	6
NFE2L2	2.49640288	0.40057637	4.01E-04	6
ERBB3	2.71942446	0.36772487	2.57E-04	5
SLC2A4	2.87769784	0.3475	0.00182828	5
CASP9	2.6618705	0.37567568	0.00251243	5
TOP2A	2.67625899	0.37365591	0.01634902	5
CHEK1	2.8705036	0.34837093	6.01E-05	5
E2F2	2.58992806	0.38611111	2.92E-04	5
CHEK2	2.58992806	0.38611111	5.62E-04	5
CTSD	3.42446043	0.29201681	7.34E-04	5
CRP	2.9352518	0.34068627	0	4
ADRB2	2.90647482	0.34405941	2.28E-04	4
LDLR	2.76978417	0.36103896	4.34E-04	4
FASLG	2.67625899	0.37365591	1.41E-04	4
KDR	2.9352518	0.34068627	0	4
PPARD	2.81294964	0.35549872	2.36E-04	4
RUNX2	2.70503597	0.36968085	0.0011736	4
INSR	2.89208633	0.34577114	5.48E-04	3
NR3C2	2.72661871	0.36675462	1.29E-04	3
COL1A1	2.72661871	0.36675462	2.83E-04	3
GJA1	2.82733813	0.35368957	0.01438849	3
PLAU	3.48920863	0.28659794	0.01438849	3
NQO1	2.96402878	0.33737864	0	3
SELE	2.98561151	0.33493976	8.63E-05	3
MPO	3.23741007	0.30888889	0	3
PRSS1	2.99280576	0.33413462	0	3
AHR	3.77697842	0.2647619	0	2
CYP1B1	4.21582734	0.23720137	1.04E-04	2

TEP1	3.77697842	0.2647619	0	2
SOD1	3.76258993	0.26577438	0.00166519	2
PIK3CG	3.30935252	0.30217391	0	2
TOP1	2.8057554	0.35641026	0	2
DRD4	3.76978417	0.26526718	0.01438849	2
GSTM1	3.28057554	0.30482456	0.01261903	2
CYP3A4	2.79856115	0.35732648	0	2
CYP1A2	2.81294964	0.35549872	0	2
NR1I3	2.74100719	0.3648294	8.34E-05	2
FOSL1	3.27338129	0.30549451	8.96E-04	2
ACACA	1	1	0	1
FASN	3.08633094	0.32400932	0	1
PON1	1	1	0	1
CA2	1	1	0	1
GSR	1	1	0	1
RASSF1	3.68345324	0.27148438	0	1
SLPI	4.76258993	0.20996979	0	1
GSTP1	3.78417266	0.26425856	0	1
F3	1	1	0	1
F7	4.48201439	0.22311396	0	1
GSTM2	3.69784173	0.27042802	0	1
HTR2A	3.49640288	0.28600823	0	1
SLC6A4	3.82014388	0.26177024	0	1
PTGS1	3.10791367	0.32175926	0	1
ODC1	1	1	0	1
PLAT	3.66906475	0.27254902	0	1

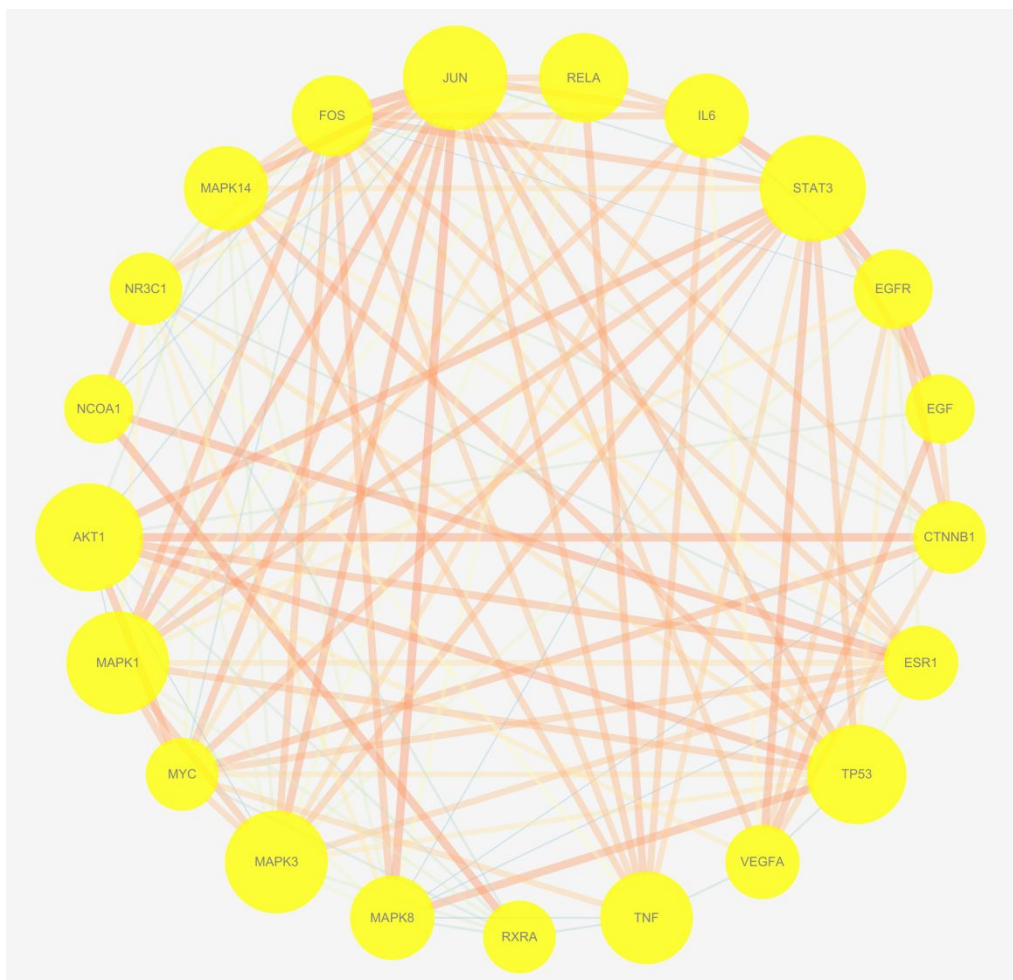


Figure S2 the PPI core network of the top 20 target genes according to degree value.