

1 **Anti-inflammation chemical constituents of *Flos Chrysanthemi Indici* determined**
2 **by UPLC-MS/MS integrated with network pharmacology**

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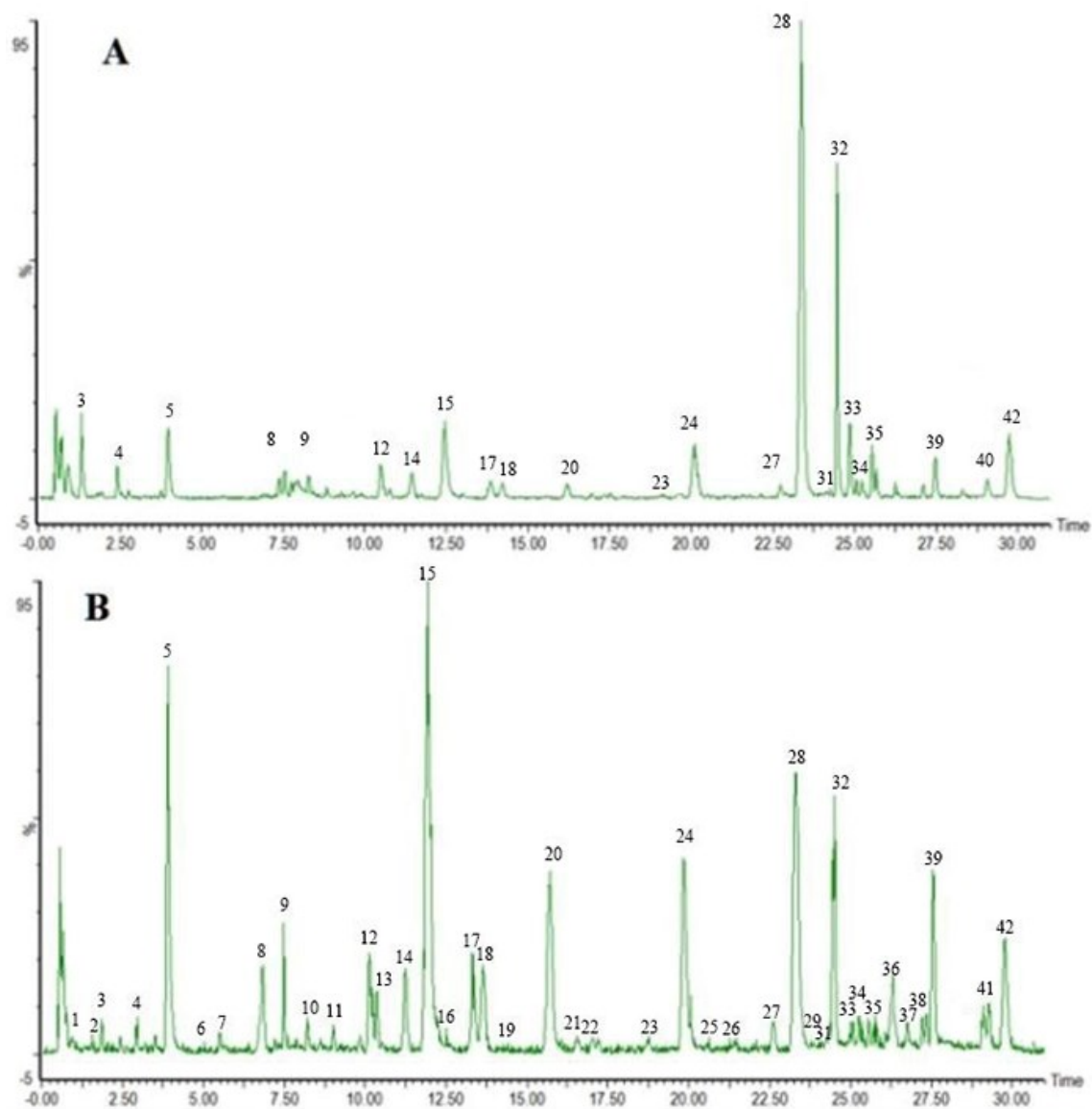
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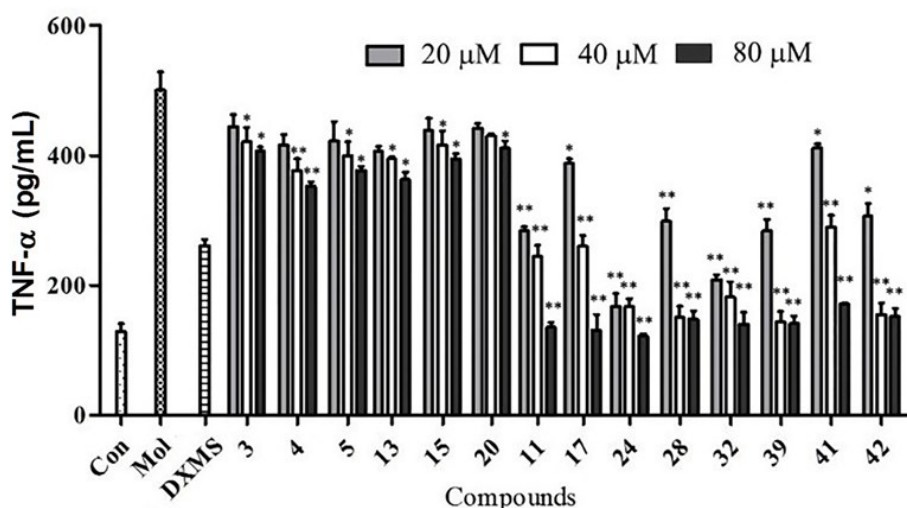
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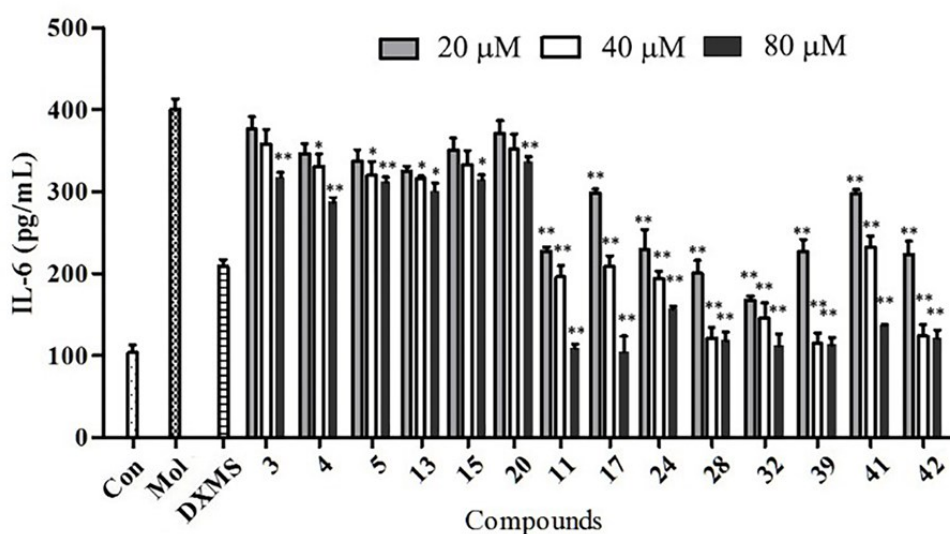
37 **Fig. S1** Typical UPLC-Q-TOF/MS base peak intensity (BPI) chromatograms of FCI in positive
38 ion mode (A) and negative ion mode (B).



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40 **Fig. S2** Effect of 14 key constituents on the production of TNF- α in LPS activated RAW264.7
 41 macrophages. Data were represented as mean \pm S.D. with three independent experiments (n = 3). *
 42 Means P < 0.05, ** means P < 0.01 compared with the only LPS treated group. Con: Control group;
 43 Mol: LPS treated group; DXMS: dexamethasone treated group.

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47 **Fig. S3** Effect of 14 key constituents on the production of IL-6 in LPS activated RAW264.7
 48 macrophages. Data were represented as mean \pm S.D. with three independent experiments (n = 3). *
 49 Means P < 0.05, ** means P < 0.01 compared with the only LPS treated group. Con: Control group;
 50 Mol: LPS treated group; DXMS: dexamethasone treated group.

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Tab. S1 The information of 97 targets related to anti-inflammatory of FCI

No.	Target	Full Name	Uniprot ID
1	ABCG2	ATP-binding cassette sub-family G member 2	Q9UNQ
2	ADA	Adenosine Deaminase	P00813
3	ADK	Adenylate kinase	P55263
4	ADORA1	Adenosine receptor A1	P30542
5	ADORA2A	Adenosine A2a receptor	P29274
6	ADORA2B	Adenosine receptor A2b	P29275
7	ADORA3	Adenosine A3 receptor	P0DMS8
8	ADRB2	Adrenergic receptor beta-2	P07550
9	AKR1B10	Aldo-keto reductase family 1 member B10	O60218
10	ALOX12	Arachidonate 12-lipoxygenase,	P18054
11	ALOX15	Arachidonate 15-lipoxygenase	P16050
12	ALOX5	Arachidonate 5-lipoxygenase	P09917
13	AMPD3	AMP deaminase 3	Q01432
14	APOH	Apolipoprotein H	P02749
15	AR	Androgen recepto	P21730
16	BACE1	Beta-secretase 1	P56817
17	CCND1	G1/S-specific cyclin-D1	P24385
18	CCND3	G1/S-specific cyclin-D3	P30281
19	CDK6	Cyclin-dependent kinase 6	Q00534
20	CDKN2A	Cyclin-dependent kinase inhibitor 2A	P42771
21	CMA1	Cyclopropane mycolic acid synthase 1	P23946
22	COL1A1	Collagen alpha-1chain	P02452
23	CSNK2A1	Casein kinase II subunit alpha, CK II alpha	P68400
24	CTSG	Cathepsin G	P08311
25	DLG4	Disks large homolog 4	P78352
26	DNMT1	DNA (cytosine-5)-methyltransferase 1	P26358
27	DOT1L	DOT1-like protein	Q8TEK3
28	EGFR	Epidermal growth factor receptor	P00533
29	ENG	Endoglin	P17813
30	EPX	Eosinophil Peroxidase	P11678
31	ESR1	Estrogen Receptor 1	P03372
32	F2R	Coagulation factor II thrombin receptor	P26824
33	F3	Coagulation Factor III, Tissue Factor	P13726
34	FASLG	Fas ligand intracellular domain	P48023
35	FGF2	Fibroblast Growth Factor 2	P15655
36	FGFR1	Fibroblast growth factor receptor 1	P11362
37	FLT1	Fms-like tyrosine kinase 1	P17948
38	GLO1	Glycolate oxidase 1	Q10CE4
39	GRIN2B	Glutamate ionotropic receptor NMDA type subunit 2B	Q13224
40	HDAC1	Histone deacetylase 1	P56517
41	IKBKB	Inhibitor of nuclear factor kappa B kinase subunit gamma	Q9Y6K9
42	IL10	Interleukin-10	Q13651
43	IL2	Interleukin-2	P04351
44	IL6	Interleukin-6	P22273
45	INSR	Insulin receptor	P06213

46	P2RY12	P2Y purinoceptor 12	Q9H244
47	P2RY2	P2Y purinoceptor 2	P35383
48	IRS1	Insulin receptor substrate 1	P35570
49	PRKCD	Protein kinase C delta type	P28867
50	ITGAM	Integrin Subunit Alpha M	P11215
51	ITPR1	Inositol 1,4,5-trisphosphate receptor type 1	P11881
52	KDR	Kinase insert domain receptor	P35968
53	PRKCQ	Protein kinase C theta type	Q04759
54	LTA4H	Leukotriene A-4 hydrolase	P24527
55	MAG	Myelin-associated glycoprotein	P07722
56	MAOA	Monoamine oxidase A	P21397
57	MAPK14	Mitogen-activated protein kinase 14	P47811
58	SCN4A	Sodium channel protein type 4 subunit alpha	P10636
59	SCN5A	Sodium channel protein type 5 subunit alpha	P34884
60	MMP12	Matrix metalloproteinase 12	P34960
61	MMP2	Matrix metalloproteinase 2	P08253
62	MMP9	Matrix metalloproteinase-9	P14780
63	SIN3A	Histone deacetylase complex subunit Sin3a	Q60520
64	STAT3	Signal transducer and activator of transcription 3	P40763
65	TBXAS1	Thromboxane-A synthase	P24557
66	NCOA2	Nuclear receptor coactivator 2	P15596
67	NFKBIA	NF-kappa-B inhibitor alpha	P25963
68	NOS2	Nitric oxide synthase, inducible	P35228
69	NOX4	NADPH oxidase 4	Q5R5C5
70	NR4A1	Nuclear receptor subfamily 4 group A member 1	P22736
71	TLR4	Toll-like receptor 4	Q9QUK6
72	TRAF1	TNF receptor-associated factor 1	P39428
73	PDE5A	Phosphodiesterase 5A	O76074
74	PKN1	Protein kinase N1	P70268
75	PLA2G1B	Phospholipase B1	P04054
76	PLA2G2A	Phospholipase A2	P14555
77	P2RY12	P2Y purinoceptor 12	P70496
78	P2RY2	P2Y purinoceptor 2	P00747
79	PPARG	Peroxisome proliferator-activated receptor gamma	P37231
80	PRKCA	Protein kinase C alpha type	P17252
81	PRKCE	Protein kinase C epsilon type	P16054
82	PRSS1	Serine Protease 1	P07477
83	PRTN3	Proteinase 3	P24158
84	PTGER2	Prostaglandin E2 receptor EP2 subtype	P43116
85	PTGES	Prostaglandin E synthase	O14684
86	PTGS1	Prostaglandin G/H synthase 1	P23219
87	PTGS2	Prostaglandin G/H synthase 2	P35354
88	QARS	Glutamine--tRNA ligase	P47897
89	RNASE1	Ribonuclease pancreatic	P07998
90	RNASE3	Ribonuclease A Family Member 3	P12724
91	SCN2A	Sodium channel protein type 2 subunit alpha	P04775
92	SELE	Selectin E	P16581
93	SELP	Selectin P	P25236

94	SERPINB2	Serpin family B member 2	P05120
95	TNF	Tumor necrosis factor	P01375
96	VEGFA	Vascular endothelial growth factor A	P15692
97	XDH	Xanthine dehydrogenase/oxidase	P47989

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58 **Tab. S2** The 29 potential anti inflammation compounds from FCI and their targets

NO.	Compound	Target
1	Quinic acid	PTGER2, PTGES, LTA4H, PRKCA, TRPM8
3	5-Caffeoylquinic acid	PRKCA, INSR, PDE5A, NR4A1, SELE
4	Caffeic acid	PTGS1, PTGS2, ADRB2
5	Chlorogenic acid	PRKCA, INSR, ADORA2B, NR4A1, SELE
6	4-Caffeoylquinic acid	PRKCA, INSR, PDE5A, NR4A1, SELE
8	Eriodictyol-7- <i>O</i> -glucoside	TNF, ADORA1, ADORA3, VEGFA
9	Rutin	TNF, PDE5A, DNMT3B, CA1, SELP, DLG4, P2RY12, RNASE2, RNASE1, MPO, ALOX15
10	Isoquercitrin	CA2, CA12, CA4, NOX4, PTGS2, CD38, PDE5A, TNF, IL2, ADORA1, ALOX5, ADORA3, ABCG2, CYP1B1, CA1, ALOX15, MMP9, MMP2
11	Luteolin-7- <i>O</i> - β -glucoside	TNF, IL2, PDE5A, P2RY2, MAPK14, PLA2G2A
12	Luteolin-7- <i>O</i> -glucuronide	TNF, IL2, PRKCA, PLA2G2A, ADORA3
13	3, 4-Dicaffeoylquinic acid	PRKCA, SELE, PDE5A, ADORA3
14	Robinin	QARS, PDE5A, ADORA3, VEGFA, PRKCA
15	3, 5-Dicaffeoylquinic acid	PRKCA, SELE, PDE5A, ADORA3
16	Quercitrin	PDE5A, ADORA1, ADORA3, P2RY2, MAG, MPO, ALOX15, PTGER2, PTGES, PRKCA
17	Apigenin-7- <i>O</i> - β -glucoside	TNF, IL2, ADORA1, PRKCA, ADORA3, PDE5A, FGFR1, TNF, IL2, PRKCA, ADORA3, MAPK14, PDE5A
19	Diosmetin-7- <i>O</i> -glucuronide	PDE5A, P2RY2, ITPR1, MAPK14
20	4, 5-Dicaffeoylquinic acid	AKR1B10, PRKCA, PDE5A
23	Quercetin	PDE5A, ADORA1, ADORA3, P2RY2, MAG, AR, MMP9, MMP2, CA4, MMP12, CD38, CYP1B1, MPO, ALOX15
24	Luteolin	NOX4, XDH, MAOA, ALOX5, GLO1, TTR, AKR1B10, ALOX15, NFKBIA, PKN1, BACE1, PLG, AR, MMP9, MMP2, CA4, MMP12, CD38, CYP1B1, ABCG2, SERPINB2, ADORA2A, PDE4D, PDE9A,

		XDH
26	Isorhamnetin	HDAC1, AMPD3, SLC5A4, CDK6, MMP9 SCN4A, SCN2A, ALOX15, PTGS2,
28	Linarin	NFKBIA, TNF, ADORA1, IL2, CA2, PRKCA, ADORA3, PRKCD, PRKCE PDE5A, PTGS1, PTGS2
30	Quercetin-3- <i>O</i> -glucuronide-7- <i>O</i> -glucoside	PDE5A, ADORA1, ADORA3, P2RY2, MAG, MPO
31	Kaempferol	MAOA, ALOX5, GLO1, AKR1B10, ALOX15, NFKBIA, PKN1, BACE1, PLG, CA4, MMP12, CD38, CYP1B, PIM1
32	Apigenin	PTGS1, PTGS2, TNF, NFKBIA, ODC1, IKBKG, ADORA3, ALOX15, INSR
35	Diosmetin	TNF, F3, SCN5A, SCN4A, SCN2A, PDE5A
36	Tricin	PLA2G2A, ALOX15
39	Jaceosidin	NOS2, PPARG, PTGS2, MAPK14, NCOA2, PLA2G2A, ADORA3, ALOX15, MPO, PLG, MMP9
41	Acacetin	NOS2, PTGS1, PTGS2, ADRB2, FASLG, ALOX15, ALOX12, ADORA3, PLA2G2A
42	Eupatilin	NOS2, PPARG, PTGS2, MAPK14, PTGS1, PLA2G2A, ADORA3, PLG, ALOX15, MMP9

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Tab. S3 Relative peak area of the 42 compounds in UPLC-Q-TOF/MS of FCI

No.	Identification	Relative peak area	Percentage of total peak area
1	Quinic acid	583	0.03
2	Maleic acid	731	0.04
3	5-Caffeoylquinic acid	9431	1.03
4	Caffeic acid	11412	1.22
5	Chlorogenic acid	158090	8.92
6	4-Caffeoylquinic acid	46351	2.61
7	Luteolin-7- <i>O</i> -rutinoside	8648	0.49
8	Eriodicyol-7- <i>O</i> -glucoside	5531	0.31
9	Rutin	1792	0.10
10	Isoquercitrin	2937	0.17
11	Luteolin-7-<i>O</i>-β-D-glucoside	49495	2.79
12	Luteolin-7- <i>O</i> -glucuronide	19527	1.10
13	3,4-Dicaffeoylquinic acid	42073	2.37
14	Robinin	352	0.02
15	3,5-Dicaffeoylquinic acid	337800	19.06
16	Quercitrin	527	0.03
17	Apigenin-7-<i>O</i>-β-D-glucoside	43242	2.44
18	Apigenin-7- <i>O</i> -rutinoside	1792	0.10
19	Diosmetin-7- <i>O</i> -glucuronide	529	0.03
20	4,5-Dicaffeoylquinic acid	133169	7.51
21	Apigenin-7- <i>O</i> -(6"- <i>O</i> -acetyl)- β -D-glucoside	579	0.03
22	Diosmetin-7- <i>O</i> -rutinoside	2971	0.17
23	Quercetin	672	0.04
24	Luteolin	133196	7.51
25	Acacetin-7- <i>O</i> -(6"- <i>O</i> - α -L-rhamnopyranosyl)- β -sophoroside	1724	0.10
26	Isorhamnetin	5741	0.32
27	Eupatolitin	5258	0.30
28	Linarin	223559	12.61
29	5, 7-Dihydroxy-4'-methoxyisoflavone	5713	0.32
30	Quercetin-3- <i>O</i> -glucuronide-7- <i>O</i> -glucoside	295	0.02
31	Kaempferol	714	0.04
32	Apigenin	110652	6.24
33	Acacetin-7- <i>O</i> - β -D-rhamnopyranosyl-(1 \rightarrow 6)-[2- <i>O</i> -acetyl-glucopyranosyl (1 \rightarrow 2)]-glucopyranoside	791	0.04
34	Chrysoeriol	5912	0.33
35	Diosmetin	5741	0.32
36	Tricin	786	0.04
37	5, 3', 4'-Trihydroxy-6, 7-dimethoxyflavone	1621	0.09
38	5, 7, 3'-Trihydroxy-6, 4', 5'-trimethoxyflavone	279	0.02
39	Jaceosidin	26315	2.16

40	Handelin	15795	0.89
41	Acacetin	87599	3.94
42	Eupatilin	68896	2.89

Tab. S4 The protein-protein interaction of 87 targets acted by 14 key constituents of FCI

No.	Target (Node 1)	Related target (Node 2)
1	ABCG2	-
2	ADA	-
4	ADORA1	P2RY12, IL6
5	ADORA2A	ADRB2, PTGER2, ADORA2B, USP4, ADORA1
6	ADORA2B	PTGER2, IL6, ALOX12
7	ADORA3	P2RY12, ADORA1, MMP2
8	ADRB2	PTGER2, ADORA2B, INSR
9	AKR1B10	ADORA1
10	ALOX12	SRD5A1, MMP2, MAPK14, PTGES ALOX12, IL6, PTGES, ADRB2, MMP2, PPARG, ODC1, EGFR,
11	ALOX15	STAT3, FLT1, MMP2, MAPK14, KDR, CCND1, PPARG, CMA1, F2R, NOX4, PTGES, NFKBIA IL6, PTGS1, LTA4H, PTGES, ADRB2, MMP2, PPARG, ODC1,
12	ALOX5	MAPK14, KDR, CCND1, PPARG, CMA1, F2R, NOX4, PTGES, NFKBIA
13	AMPD3	-
14	APOH	-
16	BACE1	MMP2
17	CCND1	MMP2, NFKBIA
18	CCND3	CDK6, PPARG, CCND1, STAT3, EGFR
19	CDK6	CCND1, STAT3, NFKBIA, MAPK14
20	CDKN2A	CCND1, CDK6, CCND3, MAPK14, VEGFA, MMP2, HDAC1, RELA
21	CMA1	MMP2
22	COL1A1	NFKBIA
23	CSNK2A1	MMP2
24	CTSG	-
25	DLG4	GRIN2B, FLT1, KDR
26	DNMT1	DNMT3B, STAT3, IL6, KDR
27	DOT1L	HDAC1
28	EGFR	STAT3, CCND1, IL6, MAPK14, MMP2, KDR, ABCG2, NFKBIA
30	EPX	-
31	ESR1	-
32	F2R	P2RY2, CCND1, PRSS1, SELP, MMP2, IL6, EGFR
33	F3	-
34	FASLG	PRKCQ, PRKCE, MAPK14
35	FGF2	-
36	FGFR1	VEGFA, CCND1, IRS1, STAT3, MMP2, MMP9, MAPK14
37	FLT1	STAT3, MMP2, EGFR, CCND1, MAPK14
38	GLO1	AKR1B10
39	GRIN2B	SIN3A

40	HDAC1	DNMT3B, DNMT1, CSNK2A1, CCND1, NFKBIA, STAT3, CDK6, CCND3, PPARG, MAPK14, EGFR
41	IKBKB	NFKBIA, PRKCQ, EGFR, PRKCE, MAPK14, NFKBIA, SELP, GRIN2B, KDR, DLG4, IL6
42	IL10	IL6, STAT3, MMP9, VEGFA, MMP2, MAPK14
43	IL2	-
44	IL6	MMP2, CCND1, MAPK14, CD38, NFKBIA, CMA1, IL10, STAT3, MMP9, VEGFA, MMP2, MAPK14, TLR4, PPARG, EGFR, RELA, NOS2
45	INSR	PPARG, STAT3, IL6, PRKCQ, DLG4, CCND1
46	P2RY12	-
47	P2RY2	-
48	IRS1	INSR, EGFR, IL6, STAT3, KDR, FLT1, PPARG, PRKCQ, CCND1, MAPK14
49	PRKCD	-
50	ITGAM	-
51	ITPR1	IL6, MMP2
52	KDR	CCND1, ABCG2, MAPK14
55	MAG	-
56	MAOA	GLO1, AKR1B10, HDAC1
57	MAPK14	NFKBIA, CCND1, MMP2, CSNK2A1
60	MMP12	-
61	MMP2	-
62	MMP9	VEGFA, IL6, EGFR, STAT3, FLT1, MMP2, MAPK14
63	SIN3A	CCND1, IL6, MAPK14, MMP2, NFKBIA, PRKCQ, KDR
64	STAT3	PTGES, PTGS1, ALOX5
65	TBXAS1	IL6, EGFR, NOX4, IKBKG, STAT3, MMP9, NOS2
66	NCOA2	AR, PPARG, CCND3, PKN1, SIN3A, IL6, MAPK14, NR4A1, ESRRA
67	NFKBIA	IKBKB, IKBKG, IRAK1, REL, RELA, TNF, BTRC, CHUK
68	NOS2	MAPK14, NFKBIA, SELP, GRIN2B, KDR, DLG4, IL6
69	NOX4	MAPK14, MMP2
70	NR4A1	PPARG, ESRRA, PTGER2, STAT3
71	TLR4	VEGFA, MMP2, INSR, IRS1, PTGES
72	TRAF1	NFKBIA, PKN1, IKBKG, CCND1, IL6
73	PDE5A	ITPR1
74	PKN1	PRKCE, MAPK14
76	PLA2G2A	ALOX12, PTGS1, ALOX15, ALOX5, PTGES, IL6
77	P2RY12	IL6, SELP, ADORA2B
78	P2RY2	ADRB2, EGFR, IL6, KDR, ADORA1
79	PPARG	ESRRA, NOX4, ABCG2, IL6, CCND1, STAT3, EGFR, MMP2, MAPK14, KDR
80	PRKCA	EGFR, NFKBIA, PRKCE, RELA, GRIN2B, PRKCD, ITPR1, IL6, PPARG, CD38, DLG4, INSR

81	PRKCD	MAPK14
82	PRKCE	EGFR, PTGER2, PPARG, IL6,
83	PRKCQ	PRKCQ, STAT3, IRS1, EGFR, MAPK14
84	PTGER2	MAPK14
85	PTGES	STAT3, IRS1, PRKCQ, NFKBIA, PRKCE, INSR, EGFR, ITPR1, ESRRA, ADRB2, MAPK14
86	PTGS1	PTGES, ALOX12, ALOX15, PTGER2, STAT3, CSNK2A1, , NOS2, MAPK14, CDK6, SERPINB2, PTGS1, NFKBIA, PPARG, STAT3, MAPK14, CCND1, PPARG, IL6, TRAF1, NOS2, MMP9, CSNK2A1, TLR4, PRKCD, IKBKG, FASLG
87	PTGS2	STAT3, MAPK14, CCND1, PPARG, IL6, TRAF1, NOS2, MMP9, CSNK2A1, TLR4, PRKCD, IKBKG, FASLG
88	QARS	HDAC1, NFKBIA
89	RNASE1	BACE1, AR, SIN3A, KDR, EGFR, FLT1
92	SELE	SCN5A, DLG4, SCN2A
93	SELP	MMP2
94	SERPINB2	DNMT3B, CSNK2A1, DNMT1, STAT3
95	TNF	CCND1, EGFR, STAT3, CDK6, HDAC1, NR4A1, CCND3, MAPK14, PKN1, IL6, PPARG, ESRRA, VEGFA, INSR, DNMT1, FLT1, TRPM8, SRD5A1, SIN3A, MMP9, MMP2
96	VEGFA	PRKCQ, STAT3, IRS1
97	XDH	ADRB2, KDR, FLT1, MMP2, EGFR, INSR, STAT3, IL6, PPARG, IRS1, DNMT1

84 -: there is no correlation with other 86 targets.