

Supporting Information

Conophylline inhibits matrix formation of fibroblasts

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Expression levels of TSG6 and pentraxin 3.

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Expression levels of genes related to PI3K-AKT pathway (AKT_UP.V1_UP in the Oncogenic gene set C6).

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Effects of CNP on the viability of NB1RGB cells.

Supplementary Table S1

Gene expression profiling in the Gene Set: REACTOME_HYALURONAN_METABOLISM.

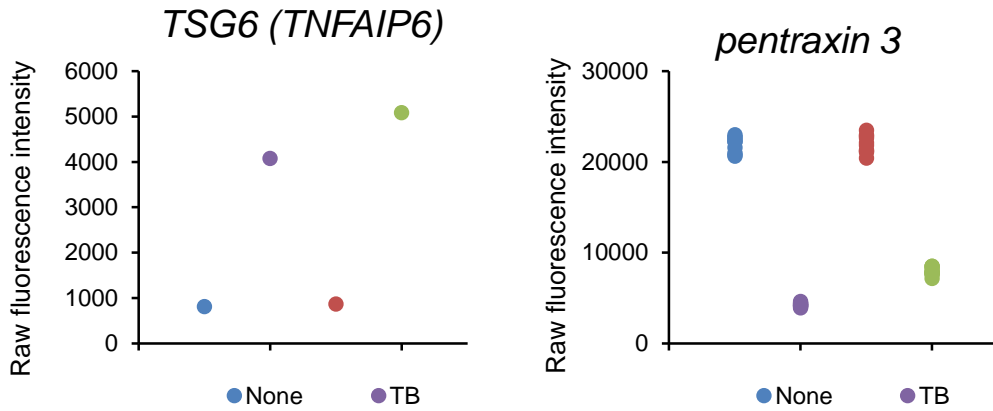
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Supplementary Table S3

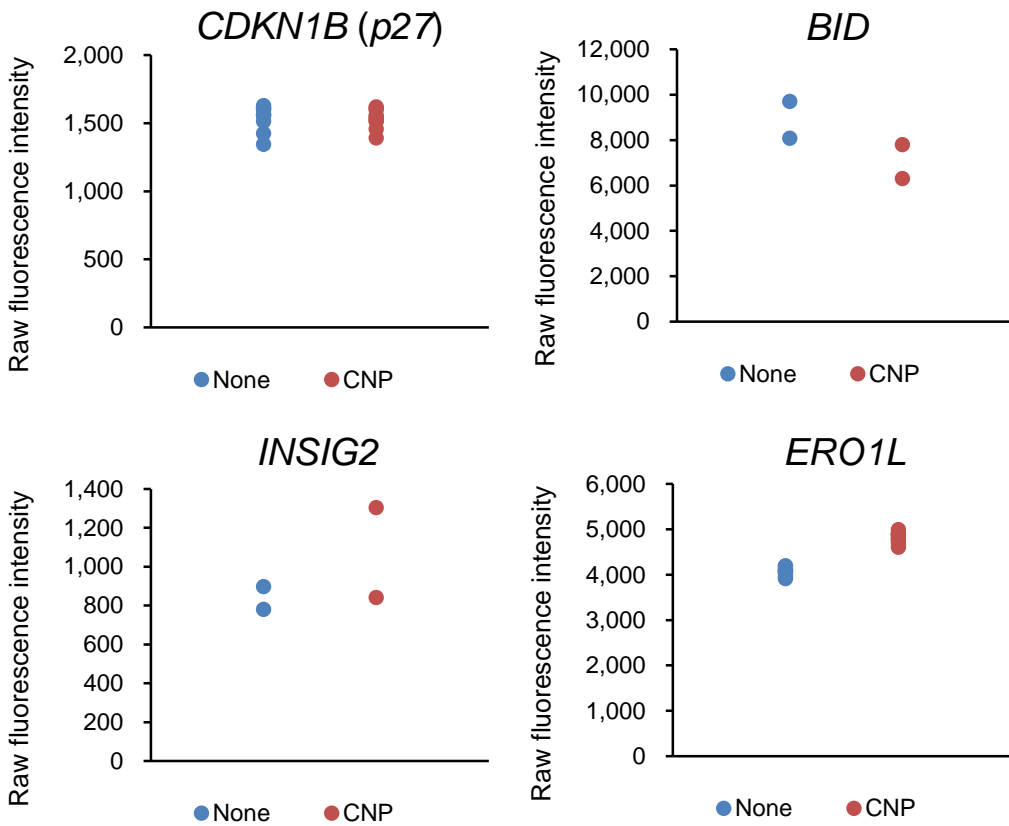
Gene expression profiling in the Gene Set: REACTOME_PI3K_AKT_ACTIVATION.

Supplementary Figure S1



Supplementary Figure S1. Expression levels of TSG6 and pentraxin 3. The graphs show the differential gene expression between CNP-treated cells and untreated cells. Raw fluorescence values obtained by scanning were utilized for comparison of gene expression of *TSG6* and *PTX3*.

Supplementary Figure S2



Supplementary Figure S2. Expression levels of genes related to PI3K-AKT pathway (AKT_UP.V1_UP in the Oncogenic gene set C6). The graphs show the differential gene expression between CNP-treated cells and untreated cells. Raw fluorescence values obtained by scanning were utilized for comparison of gene expression of *CDKN1B (p27)*, *BID*, *INSIG2*, and *ERO1L*.

Supplementary Figure S3

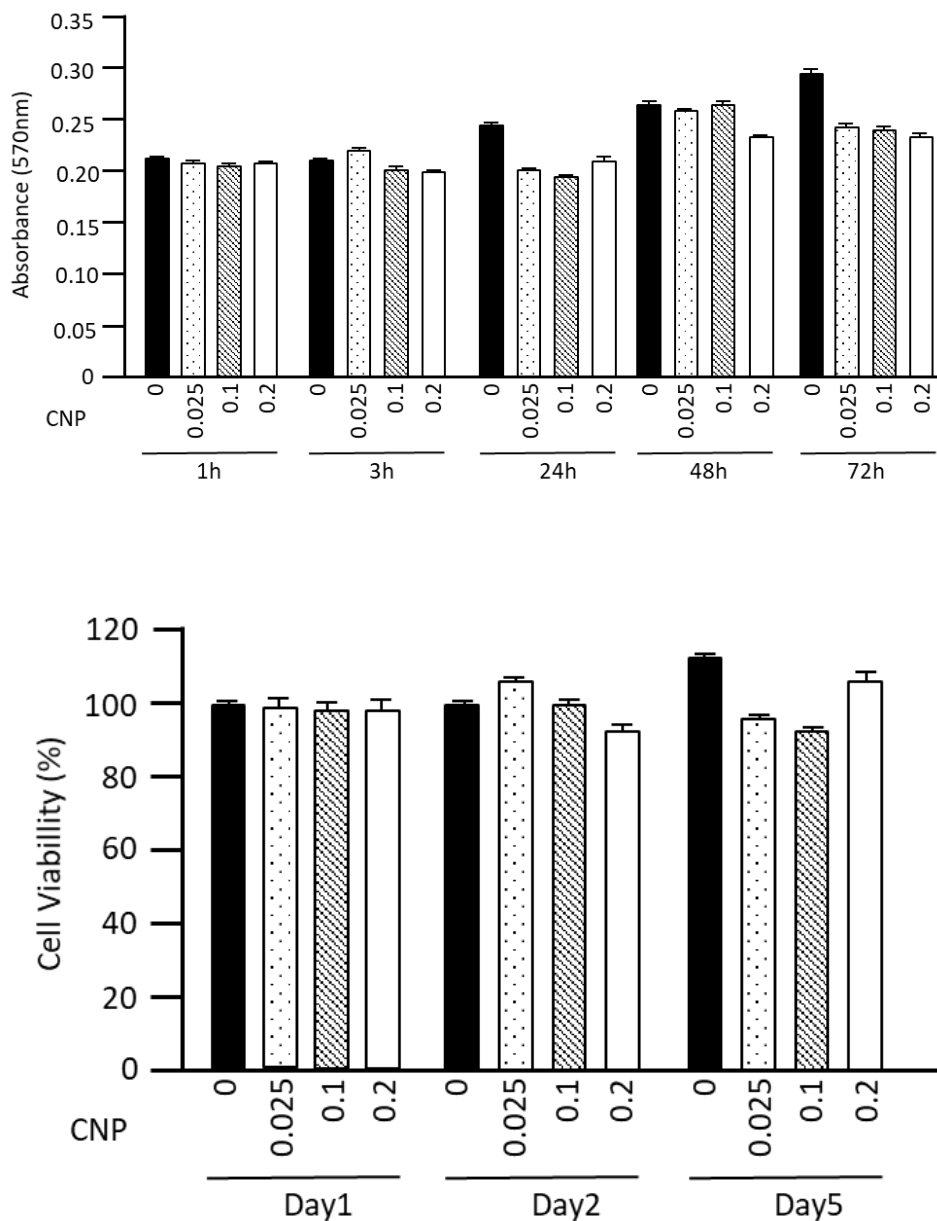


Figure 3. Effects of CNP on the viability of NB1RGB cells. NB1RGB cells at ~60% confluence treated with CNP at the concentrations as indicated ($\mu\text{g/mL}$) for days as indicated, and Trypan blue exclusion test (A) and alamarBlue assay were performed. The experiment was performed twice, with essentially the same results.

Supplementary Table S1. Gene expression profiling in the Gene Set:
 REACTOME_HYALURONAN_METABOLISM.

GeneName	Description	Normalized value		Fold change
		CNP (-)	CNP (+)	
<i>ABCC5</i>	ATP-binding cassette, sub-family C, member 5	0.65	0.87	1.7
<i>LYVE1</i>	lymphatic vessel endothelial hyaluronan receptor 1	-1.00	-1.28	0.5
<i>GUSB</i>	glucuronidase, beta	1.16	1.19	1.0
<i>HAS1</i>	hyaluronan synthase 1	1.27	0.67	0.2
<i>HAS2</i>	hyaluronan synthase 2	1.35	0.32	0.1
<i>HAS3</i>	hyaluronan synthase 3	-0.28	-0.20	1.3
<i>HEXA</i>	hexosaminidase A (alpha polypeptide)	0.93	1.00	1.2
<i>HEXB</i>	hexosaminidase B (beta polypeptide)	1.49	1.60	1.2
<i>HMMR</i>	hyaluronan-mediated motility receptor (RHAMM)	1.44	1.26	0.6
<i>HYAL1</i>	hyaluronoglucosaminidase 1	-0.69	-0.74	0.9
<i>STAB2</i>	stabilin 2	-0.35	-0.37	1.0
<i>SLC9A1</i>	solute carrier family 9, subfamily A, member 1	0.27	0.55	2.1
<i>HYAL2</i>	hyaluronoglucosaminidase 2	1.84	1.92	1.2
<i>CD44</i>	CD44 molecule (Indian blood group)	2.26	2.26	0.9

Supplementary Table S2. Gene expression profiling in the Gene Set: REACTOME_COLLAGEN_FORMATION.

GeneName	Description	Normalized value		Fold change
		CNP (-)	CNP (+)	
<i>CRTAP</i>	cartilage associated protein	-0.40	-0.49	0.8
<i>LEPREL2</i>	leprecan-like 2	2.10	2.08	0.9
<i>COL1A1</i>	collagen, type I, alpha 1	2.38	2.42	1.0
<i>COL1A2</i>	collagen, type I, alpha 2	2.58	2.63	1.0
<i>COL2A1</i>	collagen, type II, alpha 1	-1.45	-1.26	1.9
<i>COL3A1</i>	collagen, type III, alpha 1	1.21	1.13	0.8
<i>COL4A1</i>	collagen, type IV, alpha 1	1.45	1.54	1.2
<i>COL4A2</i>	collagen, type IV, alpha 2	2.19	2.21	1.0
<i>COL4A3</i>	collagen, type IV, alpha 3	-1.28	-1.28	1.1
<i>COL4A4</i>	collagen, type IV, alpha 4	-1.12	-1.12	1.1
<i>COL4A5</i>	collagen, type IV, alpha 5	-0.07	-0.10	0.9
<i>COL4A6</i>	collagen, type IV, alpha 6	-0.79	-0.67	1.4
<i>COL5A1</i>	collagen, type V, alpha 1	2.19	2.17	0.9
<i>COL5A2</i>	collagen, type V, alpha 2	1.93	1.91	0.9
<i>COL6A1</i>	collagen, type VI, alpha 1	2.56	2.60	1.0
<i>COL6A2</i>	collagen, type VI, alpha 2	1.27	1.45	1.6
<i>COL6A3</i>	collagen, type VI, alpha 3	1.31	1.42	1.3
<i>COL7A1</i>	collagen, type VII, alpha 1	0.96	0.89	0.8
<i>COL8A1</i>	collagen, type VIII, alpha 1	1.96	1.95	0.9
<i>COL8A2</i>	collagen, type VIII, alpha 2	0.63	0.46	0.6
<i>COL9A1</i>	collagen, type IX, alpha 1	-0.37	-0.34	1.1
<i>COL9A2</i>	collagen, type IX, alpha 2	-0.10	-0.09	1.1
<i>COL9A3</i>	collagen, type IX, alpha 3	-0.49	-0.57	0.9
<i>COL10A1</i>	collagen, type X, alpha 1	0.58	0.41	0.6
<i>COL11A1</i>	collagen, type XI, alpha 1	-1.13	-1.16	1.0
<i>COL11A2</i>	collagen, type XI, alpha 2	0.20	0.16	0.9
<i>COL12A1</i>	collagen, type XII, alpha 1	2.16	2.18	0.9
<i>COL13A1</i>	collagen, type XIII, alpha 1	1.04	0.93	0.7
<i>COL15A1</i>	collagen, type XV, alpha 1	-0.30	-0.26	1.2
<i>COL16A1</i>	collagen, type XVI, alpha 1	1.78	1.68	0.7
<i>COL17A1</i>	collagen, type XVII, alpha 1	-1.08	-1.12	0.9
<i>COL19A1</i>	collagen, type XIX, alpha 1	-1.47	-1.46	1.1
<i>ADAMTS14</i>	ADAM metalloproteinase with thrombospondin type 1 motif, 14	0.18	0.01	0.7
<i>COL22A1</i>	collagen, type XXII, alpha 1	-1.35	-1.34	1.1
<i>GLT25D2</i>	glycosyltransferase 25 domain containing 2	0.05	-0.06	0.8
<i>COL24A1</i>	collagen, type XXIV, alpha 1	-0.64	-0.94	0.5
<i>PCOLCE2</i>	procollagen C-endopeptidase enhancer 2	0.83	0.70	0.7
<i>COL28A1</i>	collagen, type XXVIII, alpha 1	-0.11	-0.10	1.0
<i>P4HB</i>	prolyl 4-hydroxylase, beta polypeptide	2.38	2.41	1.0
<i>COL5A3</i>	collagen, type V, alpha 3	0.50	0.56	1.2
<i>PCOLCE</i>	procollagen C-endopeptidase enhancer	1.44	1.54	1.3
<i>PLOD1</i>	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1	1.11	1.22	1.3
<i>PLOD2</i>	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	1.77	1.94	1.5
<i>PP1B</i>	peptidylprolyl isomerase B (cyclophilin B)	1.70	1.79	1.2
<i>LEPREL1</i>	leprecan-like 1	0.95	0.97	1.0
<i>BMP1</i>	bone morphogenetic protein 1	0.34	0.42	1.3
<i>TLL1</i>	tolloid-like 1	-1.00	-0.96	1.1
<i>TLL2</i>	tolloid-like 2	-1.26	-1.22	1.2
<i>COL14A1</i>	collagen, type XIV, alpha 1	-0.15	-0.14	1.1
<i>GLT25D1</i>	glycosyltransferase 25 domain containing 1	0.21	0.25	1.2
<i>COL21A1</i>	collagen, type XXI, alpha 1	-0.79	-0.44	2.6
<i>COL25A1</i>	collagen, type XXV, alpha 1	-0.75	-0.76	1.0
<i>COL27A1</i>	collagen, type XXVII, alpha 1	1.09	0.87	0.6
<i>SERPINH1</i>	serpin peptidase inhibitor, clade H, member 1	2.21	2.16	0.8
<i>PLOD3</i>	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	1.89	1.91	1.0
<i>COL23A1</i>	collagen, type XXIII, alpha 1	0.61	0.70	1.3
<i>ADAMTS2</i>	ADAM metalloproteinase with thrombospondin type 1 motif, 2	-0.32	-0.33	1.0
<i>ADAMTS3</i>	ADAM metalloproteinase with thrombospondin type 1 motif, 3	-0.48	-0.65	0.7

Supplementary Table S3. Gene expression profiling in the Gene Set: REACTOME_P13K_AKT_ACTIVATION.

GeneName	Description	Normalized value		Fold change
		CNP (-)	CNP (+)	
<i>AKT1</i>	v-akt murine thymoma viral oncogene homolog 1	1.32	1.39	1.16
<i>AKT2</i>	v-akt murine thymoma viral oncogene homolog 2	0.05	-0.23	0.49
<i>AKT3</i>	v-akt murine thymoma viral oncogene homolog 3	1.30	1.23	0.79
<i>CDKN1A</i>	cyclin-dependent kinase inhibitor 1A	0.49	0.90	3.00
<i>CDKN1B</i>	cyclin-dependent kinase inhibitor 1B	0.57	0.62	1.13
<i>CHUK</i>	conserved helix-loop-helix ubiquitous kinase	1.25	1.23	0.88
<i>THEM4</i>	thioesterase superfamily member 4	0.18	0.21	1.10
<i>CREB1</i>	cAMP responsive element binding protein 1	0.66	0.76	1.27
<i>FOXO1</i>	forkhead box O1	-0.33	-0.09	1.99
<i>FOXO3</i>	forkhead box O3	1.72	1.83	1.24
<i>FOXO4</i>	forkhead box O4	-0.55	0.30	11.34
<i>PHLPP1</i>	PH domain and leucine rich repeat protein phosphatase 1	-0.19	-0.05	1.51
<i>MTOR</i>	mechanistic target of rapamycin	0.60	0.77	1.57
<i>RICTOR</i>	RPTOR independent companion of MTOR, complex 2	0.68	0.59	0.76
<i>GSK3A</i>	glycogen synthase kinase 3 alpha	1.71	1.71	0.94
<i>NR4A1</i>	nuclear receptor subfamily 4, group A, member 1	-0.89	-1.00	0.82
<i>IRS1</i>	insulin receptor substrate 1	0.74	0.58	0.65
<i>IRS2</i>	insulin receptor substrate 2	1.90	2.05	1.37
<i>RHOA</i>	ras homolog family member A	0.63	0.47	0.64
<i>MDM2</i>	MDM2 oncogene, E3 ubiquitin protein ligase	0.24	0.14	0.78
<i>NGF</i>	nerve growth factor	-0.55	-0.70	0.72
<i>NTRK1</i>	neurotrophic tyrosine kinase, receptor, type 1	0.94	1.15	1.70
<i>PDPK1</i>	3-phosphoinositide dependent protein kinase 1	0.50	0.57	1.18
<i>PIK3CA</i>	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	-0.38	-0.28	1.32
<i>PIK3CB</i>	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit beta	0.68	1.04	2.57
<i>PIK3R1</i>	phosphoinositide-3-kinase, regulatory subunit 1	1.77	1.81	1.03
<i>PIK3R2</i>	phosphoinositide-3-kinase, regulatory subunit 2	1.19	1.18	0.95
<i>BAD</i>	BCL2-associated agonist of cell death	0.56	0.68	1.33
<i>PTEN</i>	phosphatase and tensin homolog	1.14	0.72	0.31
<i>TRIB3</i>	tribbles pseudokinase 3	1.48	1.53	1.09
<i>RPS6KB2</i>	ribosomal protein S6 kinase, 70kDa, polypeptide 2	0.96	0.92	0.89
<i>MLST8</i>	MTOR associated protein, LST8 homolog	0.46	0.59	1.42
<i>TSC2</i>	tuberous sclerosis 2	0.42	0.38	0.91
<i>MAPKAP1</i>	mitogen-activated protein kinase associated protein 1	0.35	0.52	1.59
<i>CASP9</i>	caspase 9, apoptosis-related cysteine peptidase	0.87	0.88	1.02
<i>AKT1S1</i>	AKT1 substrate 1	1.14	1.17	1.06