

Supplementary material

1. Supplementary Tables

1.1 Table S1. Concentrations of various blood components in WT and 5 × FAD mice (ng/mL)

Group	Time (h)	Animal ID	Caffeic acid	Echinac side	Verbasc oside	Cistan oside F	Isoverbas coside	Hydrox ytyrosol	Tubulosi de A	8-Epi-Log anic acid	Tubuloside B
WT	0	C97	ND	2	< LOD	ND	0.357	ND	0.277	ND	0.147
		C22	ND	2.94	< LOD	ND	0.167	ND	0.241	ND	0.0339
		C24	ND	0.128	< LOD	ND	0.0485	ND	0.0319	ND	0.0492
		B66	53.2	909	28.7	1.19	6.65	ND	24.7	5.13	0.315
	0.5	B68	35.3	661	19.2	0.961	5.16	ND	15.6	2.84	0.257
		B69	68.5	804	26.7	1.11	6.18	ND	21.3	2.39	0.264
		C30	91.4	1190	29.1	1.32	6.92	ND	26.3	3.78	0.471
		B70	0.902	235	3.51	0.531	1.16	ND	5.8	0.812	0.0151
	1	C22	ND	125	1.35	0.506	0.623	22.6	2.91	ND	0.108
		C4	ND	170	2.73	0.526	0.876	6.23	3.14	1.98	0.00699
		C98	21.2	331	7.05	0.591	1.58	1.82	7.34	0.856	0.159
		B71	ND	61.7	0.261	0.524	0.223	51.3	0.829	0.826	0.0051
	2	C8	4.3	109	2.11	0.59	0.586	6.51	1.85	0.739	0.0372
		C16	13	342	6.74	0.917	2.08	34.9	4.91	2.08	0.177
		C99	5.42	109	4.53	0.803	1.05	26.8	1.6	ND	0.101
		C17	ND	50.1	8.93	1.15	1.9	59.6	0.565	ND	0.0163
	4	C19	ND	89.4	0.815	0.377	3.24	79.1	1.46	ND	< LOD
		C20	ND	9.93	< LOD	ND	0.187	596	0.28	ND	< LOD
		B32	ND	138	19.6	1.54	3.71	436	1.26	ND	0.551
		B38	ND	1.16	ND	ND	< LOD	6.58	0.113	ND	< LOD
	0	B39	ND	1.72	< LOD	ND	0.0582	1.82	0.0549	ND	< LOD
		B41	ND	1.28	ND	ND	< LOD	1.28	0.0704	ND	< LOD
		B35	65.3	1350	38.1	1.61	7.26	ND	27.6	5.41	0.413
		B36	ND	863	23.8	1.03	10.7	ND	15.1	5.27	0.261
	0.5	B37	ND	850	22.6	1.05	3.96	1.6	18.3	4.26	0.299
		B42	ND	960	32	1.79	5.04	ND	21.3	4.93	0.178
		C35	ND	394	12	0.679	2.51	1.28	9.76	4.07	0.228
		C36	ND	483	15	0.962	2.29	5.7	9.07	3.81	0.144
	1	C37	ND	744	25.5	1.38	3.58	27.2	14.2	5.84	0.243
		C54	ND	595	20.2	1.49	3.11	129	9.69	5.3	0.263
		B73	ND	681	44.4	2.49	6.13	51.1	13.3	0.937	0.383
		C38	ND	286	24.3	1.97	4.68	73.8	8.72	0.732	0.501
	2	C40	ND	353	15.7	1.62	4.13	3.72	6.71	0.733	0.14
		C51	ND	429	6.53	0.981	1.72	113	7.13	0.954	0.0906
		C41	171	182	20.2	2.14	1.46	7.35	4.72	0.843	0.0349
		C42	ND	6.17	0.6	0.416	0.0528	66.5	0.184	ND	< LOD
	4	C43	11.4	108	10.9	1.02	3.1	68.3	1.79	ND	0.0712
		C53	188	48.5	2.29	1.08	0.357	436	1.18	ND	< LOD
		quantit ative	10	2	5	2	5	2	5	2	2

The table presents the concentrations of blood components in WT and 5 × FAD mice at different time points."ND" indicates that the component was not detected at the time point. "< LOD" indicates that the concentration was below the limit of detection.

1.2 Table S2. Screening results of disease-drug-target interactions for network pharmacology analysis.

CCH															Tubuloside B
GeneCards database										OMIM database					SwissTarget Prediction
DDC	EPO	MB	GRK2	VWF	PGF	ABCD1	EDNRB	CLLS3	SLC17A5	CTRC	CYBB	CANDF7	IGS1	MCMTTC	SPHK2
MMP7	GFAP	RPS27A	GRP	CERNA3	GDF15	MT-TL1	CDKN3	CERCAM	MIR424	GFI1	SLC6A8	SGO	MBP1	PENTT	ENPP2
FOXP2	EDN1	AFP	C5	SOD2-OT1	MMP13	CBS	CLU	FNBP1	SST	ALG14	BCAP31	AGS1	CPSQ3	CD32	DNM1
PDP1	AGT	MAOB	ADORA3	GLA	TREM1	MMP9	RBP4	CUBN	GNAS	FCGR2A	CCCSX	QARS	ARMD7	MEPCA	CHRM4
GCG	TTN	ADORA1	SAA4	CAT	MAP1B	BCL2	PWAR1	MBL2	PARP1	NCF2	CLCR	TFAR15	DBM	TNFA	CHRM5
SFTPA2	CSF3	RPL36A HNRNP2	PWAR4	SNCA	OXT	BDNF	MIR320A	ADD3	ERCC2	COPD	ZNF163	CLOVE	CGD3	SCN2	CHRM2
BECN1	TTR	HTR3A	MYOCD	S100B	FABP2	INS	SIRT1	HTRA1	GLUL	IL1R1	CMS15	PDGFR	AMCBX2	IDDEBF	CHRM1
SULT1A3	CCL2	MYOC	FBLN5	MIR195	SERPINB2	SOD1	ACE2	CLLS1	PGR-AS1	IL1RN	IGFR2	CRMO3	CCDS1	CRMO2	CHRM3
HRH2	AGTR1	MIR34C	ABCB7	PON1	SLC6A3	SHANK2	GJB2	FOLR1	GAS5	STAT1	CADASIL1	DIRA	DXS1357E	IMD31B	BCHE
TMCO1	ADRB2	SLC2A3	SRF	NFKB1	GSTM1	IGFBP7	APOL1	CLLS5	ANGPT2	SGOL1	PRIP	IMD31A	MBL2D	CAID	MET
AMBP	VEGFA	RMRP	ADRA2A	F3	GRN	TAC3	MIR181C	CMTS	C11orf65	TREX1	ARMD11	SGO1	CARASIL	HERNS	GRIN1
INPP5D	NPPA	SFTPA1	CNBP	B2M	HIF1A	OGA	COL1A1	CLUU1OS	CD34	QARS1	AAA	CRV	MBPD	MSCCA	GRIN2A
EPX	SERPINE1	CHI3L1	MMP10	TGFB2	PLA2G6	ECM1	CHRNA3	CLUU1	SERPIN1	PDCD10	CEDNIK	GLNRS	CADASIL2	CLAPO	SMO
BSG	GPT	XRCC1	SLC5A1	CALCA	CHAT	NCOA3	SFTPD	CLLS2	TSPO	PIK3CA	CML	CCM3	IMD34	MCM	CYP19A1
SLC6A2	REN	DYNC2H1	PTAFR	TSC1	BACE1	LOC109 504728	GSTT1	CLLD6	KDR	PDGFRB	HMOX1D	MCAP	AD1	IMF1	CCNE2
COL18A1	APOB	LRP2	BPI	GSTP1	ADAMTS13	AGO2	OTC	TTC5	TARDBP	CLLS4	P40PHOX	IBGC4	LMNS	SPDA1	CDK2
RNU4ATAC	MIR132	FABP1	CYP11B1	COL1A2	ABCC8	VASP	DBH	PRKCH	ATP1A2	CTEPH1	CGDX	TBN	NEDMVIC	NEDMLHB	ADRA1D
SLC2A4	GBA1	CS	ACP3	EDNRA	ENO2	STH	NAGLU	GATM	GSN	HLA-B	CRTR	C7orf22	IMF2	MGC4067	ADRA1A
DMPK	PLAT	TRA-TGC7-1	AOC1	EGF	PSEN2	C1D	HCRT	CYBA	DNMT1	TNF	BAP31	CGD1	CASIL	KIAA0172	ADRA1B
ITIH4	ELN	LTBP2	MIR124-1HG	PDGFB	NOS1	GLRA1	GNB3	CYBC1	ACHE	HLA-DPB1	D13S25	CHDS7	KURU	BDPLT10	KDR
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The table shows the potential targets of Tubuloside B(Tub-B) for treating chronic cerebral hypoperfusion (CCH). Abbreviations: Gene Symbol, official gene symbol.

2. Supplementary Figures

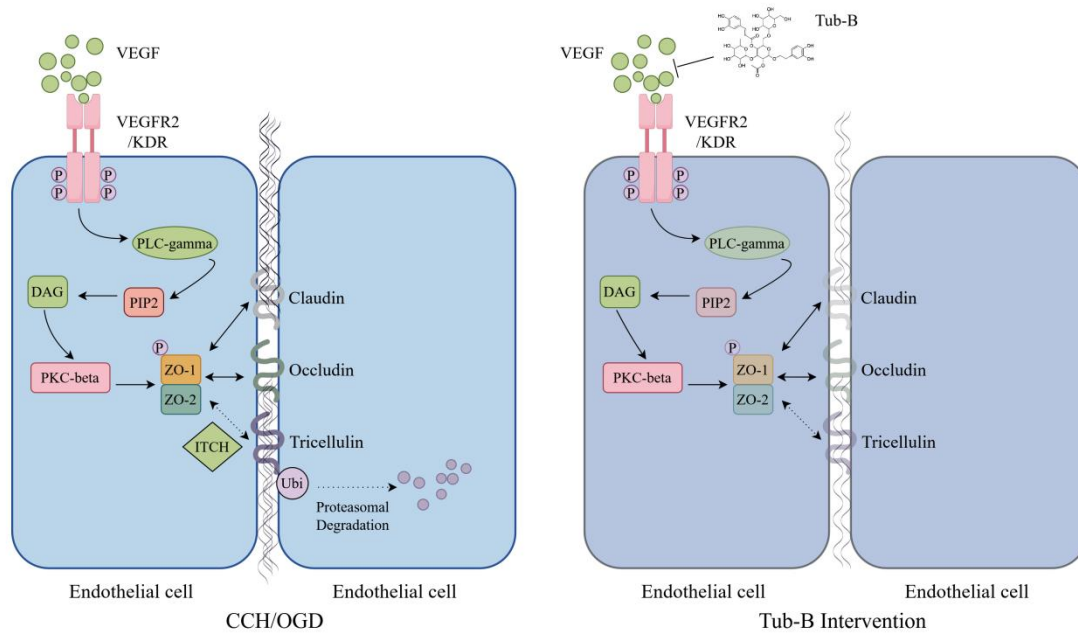


Figure S1. Schematic diagram illustrating the neuroprotective mechanism of Tubuloside B against CCH.

Tub-B protects against $A\beta$ toxicity, inhibits apoptosis and Caspase-3/7 activation, stabilizes TRIC protein, reduces its ubiquitination-mediated degradation, preserves BBB integrity, and improves learning and memory function.