

Supplementary Materials

Xanthohumol Protects Against Neuronal Excitotoxicity and Mitochondrial Dysfunction in APP/PS1 Mice: An Omics-Based Study

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● Supplementary methods

1. Gene sets for GSVA score calculation

We performed GSVA to estimate the global level of the activity of glutamatergic neuron and other types of neuron. The gene sets used for GSVA score estimation are shown below.

The gene sets used for estimation of GSVA score.

Description	Short name	Gene sets (proteins detected in our data were underlined)
SN1 and GLNT	SN1&GLNT	Slc38a1 and <u>Slc38a2</u>
Glutamate bio-synthesis	GLS	<u>Gls</u> and <u>Gls2</u>
Endocytosis	Endocytosis	Dnm1,Ap2b1,Clta, <u>Dnm2</u> , <u>Dnm3</u> , <u>Ap2a1</u> , <u>Ap2a2</u> , <u>Ap2m1</u> , <u>Ap2s1</u> , <u>Cltc</u> , <u>Cltb</u>
Vacuolar H ⁺ -adenosine triphosphatases	V-ATPase	Atp6v1b1,Atp6v0b,Atp6v1a,Atp6v0e,Atp6v0a1,Atp6v0a4,Atp6v0d2,Tcirg1,Atp6v1g3,Atp6v1c2,Atp6v1e2,Atp6v0e2, <u>Atp6v0c</u> , <u>Atp6v0a2</u> , <u>Atp6v1h</u> , <u>Atp6v1b2</u> , <u>Atp6v0d1</u> , <u>Atp6v1e1</u> , <u>Atp6v1f</u> , <u>Atp6v1g2</u> , <u>Atp6v1g1</u> , <u>Atp6v1c1</u> , <u>Atp6v1d</u>
Glutamate packaging into vesicles	vGLUT	<u>Slc17a6</u> , <u>Slc17a7</u> , and <u>Slc17a8</u>
Neurotransmitter transporter	NT-Transporter	Slc18a1,Slc18a3,Slc17a8,Slc6a4,Slc1a2,Slc1a6,Slc1a7, <u>Slc17a6</u> , <u>Slc18a2</u> , <u>Slc32a1</u> , <u>Slc17a7</u> , <u>Slc6a13</u> , <u>Slc6a9</u> , <u>Slc1a1</u> , <u>Slc1a3</u> , <u>Slc6a2</u> , <u>Slc6a1</u> , <u>Slc6a7</u> , <u>Slc6a11</u>
Exocytosis	Exocytosis	Unc13c,Unc13b,Stx2,Stx3,Cplx4, <u>Nsf</u> , <u>Vamp2</u> , <u>Syt1</u> , <u>Rab3a</u> , <u>Rims1</u> , <u>Unc13a</u> , <u>Stxbp1</u> , <u>Stx1a</u> , <u>Stx1b</u> , <u>Snap25</u> , <u>Cplx1</u> , <u>Cplx2</u> ,and <u>Cplx3</u>
Guanine nucleotide-binding protein	Gi/o	Gng14,Gnb3,Gng7,Gngt2, <u>Gnai1</u> , <u>Gnai2</u> , <u>Gnai3</u> , <u>Gnao1</u> , <u>Gnb1</u> , <u>Gnb2</u> , <u>Gnb4</u> , <u>Gnb5</u> , <u>Gngt1</u> , <u>Gng10</u> , <u>Gng12</u> , <u>Gng2</u> , <u>Gng3</u> , <u>Gng4</u> , <u>Gng5</u> , <u>Gng13</u> , <u>Gng11</u>
Ionotropic glutamate receptors	iGluR	<u>Gria1</u> , <u>Gria2</u> , <u>Gria3</u> , <u>Gria4</u> , <u>Grin1</u> , <u>Grin2a</u> ,Grin2b,Grin2c,Grin2d,Grin3a,Grin3b

Metabotropic glutamate receptors	mGluR	<u>Grm4</u> , <u>Grm6</u> , <u>Grm1</u> , <u>Grm2</u> , <u>Grm3</u> , <u>Grm5</u> , <u>Grm7</u> ,and <u>Grm8</u>
Postsynaptic glutamate receptors	Glutamate receptors	<u>Grm4</u> , <u>Grm6</u> , <u>Gria2</u> , <u>Grin2c</u> , <u>Gri</u> <u>n2d</u> , <u>Grin3a</u> , <u>Grin3b</u> , <u>Grm1</u> , <u>Grm</u> <u>2</u> , <u>Grm3</u> , <u>Grm5</u> , <u>Grm7</u> , <u>Grm8</u> , <u>Gri</u> <u>a1</u> , <u>Gria3</u> , <u>Gria4</u> , <u>Grin1</u> , <u>Grin2a</u>
Postsynaptic dopaminergic receptors	Dopaminergic receptors	<u>Drd1</u> , <u>Drd5</u> , <u>Cacna1d</u> , <u>Cacna1b</u> , <u>Kcnj5</u> , <u>Kcnj9</u> , <u>Drd3</u> , <u>Drd4</u> , <u>Drd2</u> , <u>Scn1a</u> , <u>Cacna1c</u> , <u>Cacna1a</u> , <u>Kcnj</u> <u>3</u> , <u>Kcnj6</u>
Postsynaptic cholinergic receptors	Cholinergic receptors	<u>Chrm5</u> , <u>Chrm3</u> , <u>Kcnq3</u> , <u>Kcnj12</u> , <u>Kcnj2</u> , <u>Kcnj4</u> , <u>Kcnq1</u> , <u>Kcnq2</u> , <u>Kc</u> <u>nj14</u> , <u>Kcnq5</u> , <u>Kcnq4</u> , <u>Chrm2</u> , <u>Chr</u> <u>nb4</u> , <u>Chrna3</u> , <u>Chrna4</u> , <u>Chrna6</u> , <u>Ch</u> <u>rna7</u> , <u>Chrb2</u> , <u>Cacna1d</u> , <u>Cacna1s</u> <u>,Cacna1f</u> , <u>Chrm1</u> , <u>Kcnj3</u> , <u>Kcnj6</u> , <u>Chrm4</u> , <u>Cacna1c</u> ,
Postsynaptic GABAergic receptors	GABAergic receptors	<u>Gabra6</u> , <u>Gabrb2</u> , <u>Gabre</u> , <u>Gabrg1</u> , <u>Gabrp</u> , <u>Gabrq</u> , <u>Gabrr1</u> , <u>Gabrr2</u> , <u>G</u> <u>abrr3</u> , <u>Cacna1b</u> , <u>Cacna1d</u> , <u>Cacna</u> <u>1s</u> , <u>Cacna1f</u> , <u>Gabbr1</u> , <u>Gabbr2</u> , <u>Ga</u> <u>bra5</u> , <u>Gabra1</u> , <u>Gabra2</u> , <u>Gabra3</u> , <u>G</u> <u>abra4</u> , <u>Gabrb1</u> , <u>Gabrb3</u> , <u>Gabrd</u> , <u>G</u> <u>abrg2</u> , <u>Gabrg3</u> , <u>Slc12a5</u> , <u>Cacna1</u> <u>a</u> , <u>Cacna1c</u> , <u>Kcnj6</u>
Postsynaptic serotonergic receptors	Serotonergic receptors	<u>Cacna1d</u> , <u>Cacna1s</u> , <u>Cacna1f</u> , <u>Htr</u> <u>2a</u> , <u>Htr2b</u> , <u>Htr2c</u> , <u>Htr3a</u> , <u>Htr3b</u> , <u>Ht</u> <u>r4</u> , <u>Htr6</u> , <u>Htr7</u> , <u>Htr1b</u> , <u>Htr1d</u> , <u>Htr1</u> <u>f</u> , <u>Htr5a</u> , <u>Htr5b</u> , <u>Cacna1b</u> , <u>Kcnj3</u> , <u>Kcnj5</u> , <u>Kcnj9</u> , <u>Cacna1c</u> , <u>Htr1a</u> , <u>C</u> <u>acna1a</u> , <u>Kcnj6</u>
GABA type A receptor	GABA _A R	<u>Gabra6</u> , <u>Gabrb2</u> , <u>Gabre</u> , <u>Gabrg1</u> , <u>Gabrp</u> , <u>Gabrq</u> , <u>Gabra5</u> , <u>Gabra1</u> , <u>Gabra2</u> , <u>Gabra3</u> , <u>Gabra4</u> , <u>Gabrb</u> <u>1</u> , <u>Gabrb3</u> , <u>Gabrd</u> , <u>Gabrg2</u> , <u>Gabrg</u> <u>3</u>

● Supplementary figures

Figure S1

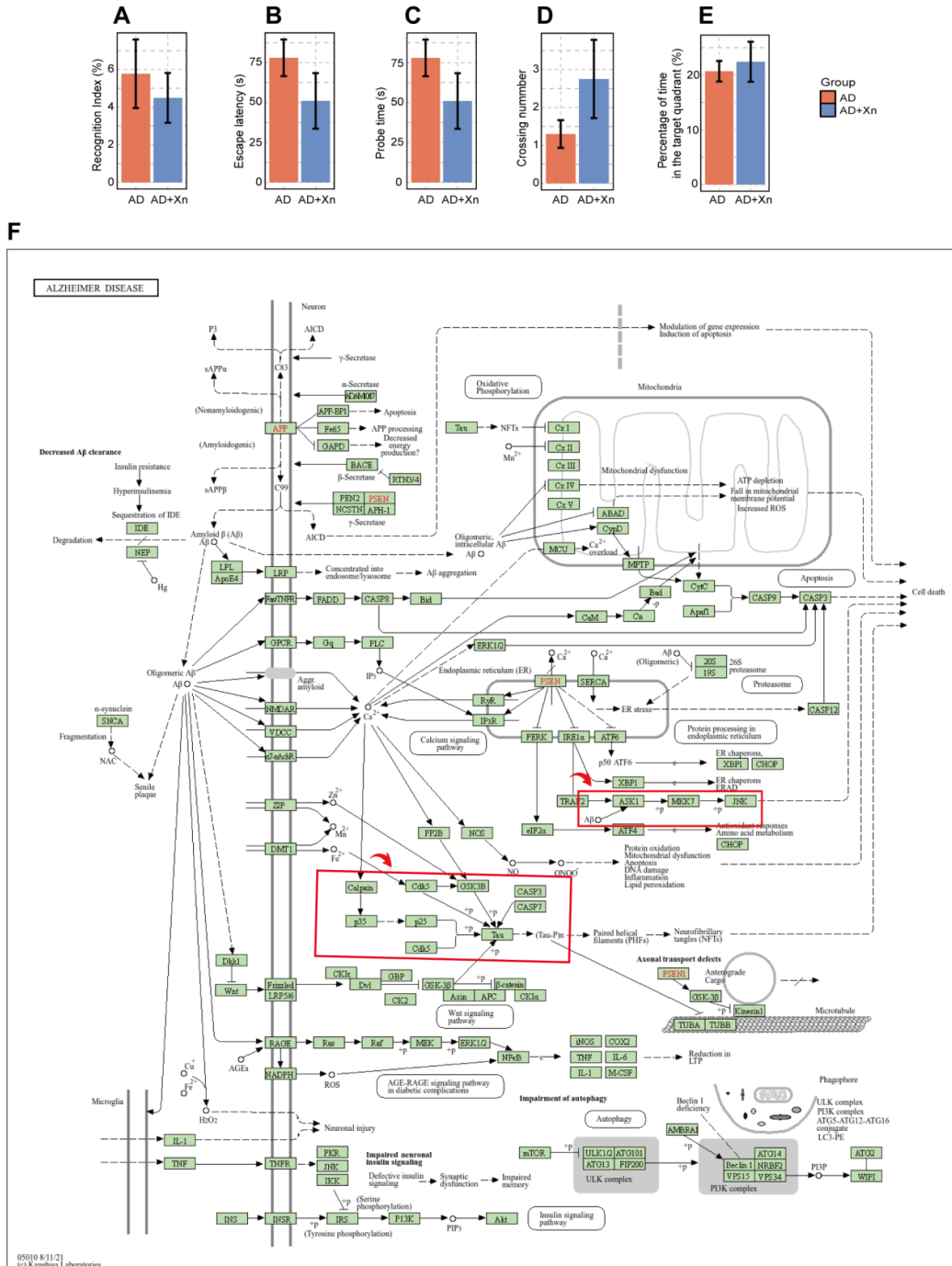


Figure S1. The behavioral performance of AD mice and the ‘Alzheimer’s disease’ pathway in the KEGG database. (A) The baseline novel object recognition test (new object exploration time/total exploration time × 100%) (n = 9-10 per group,

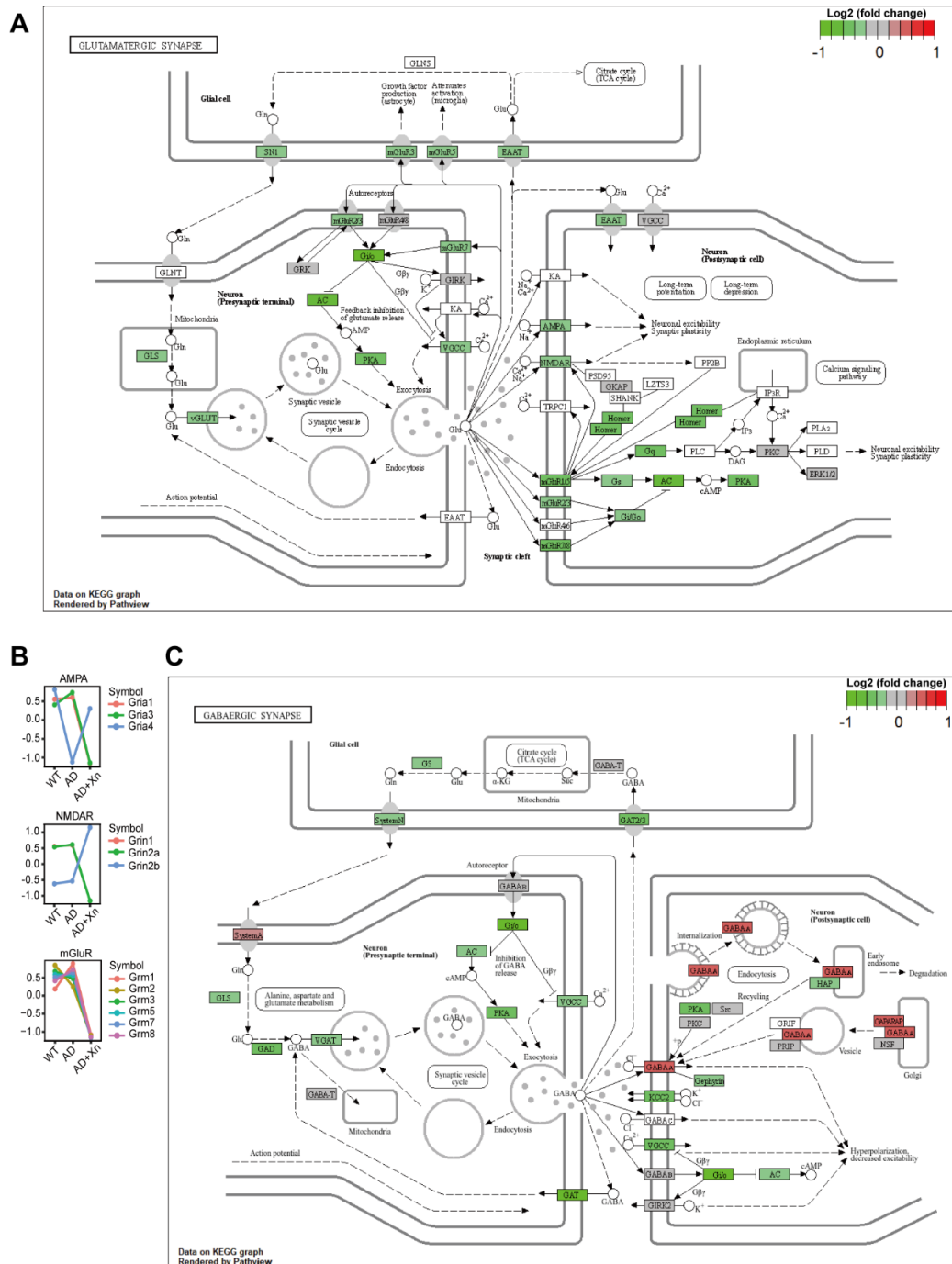


Figure S4

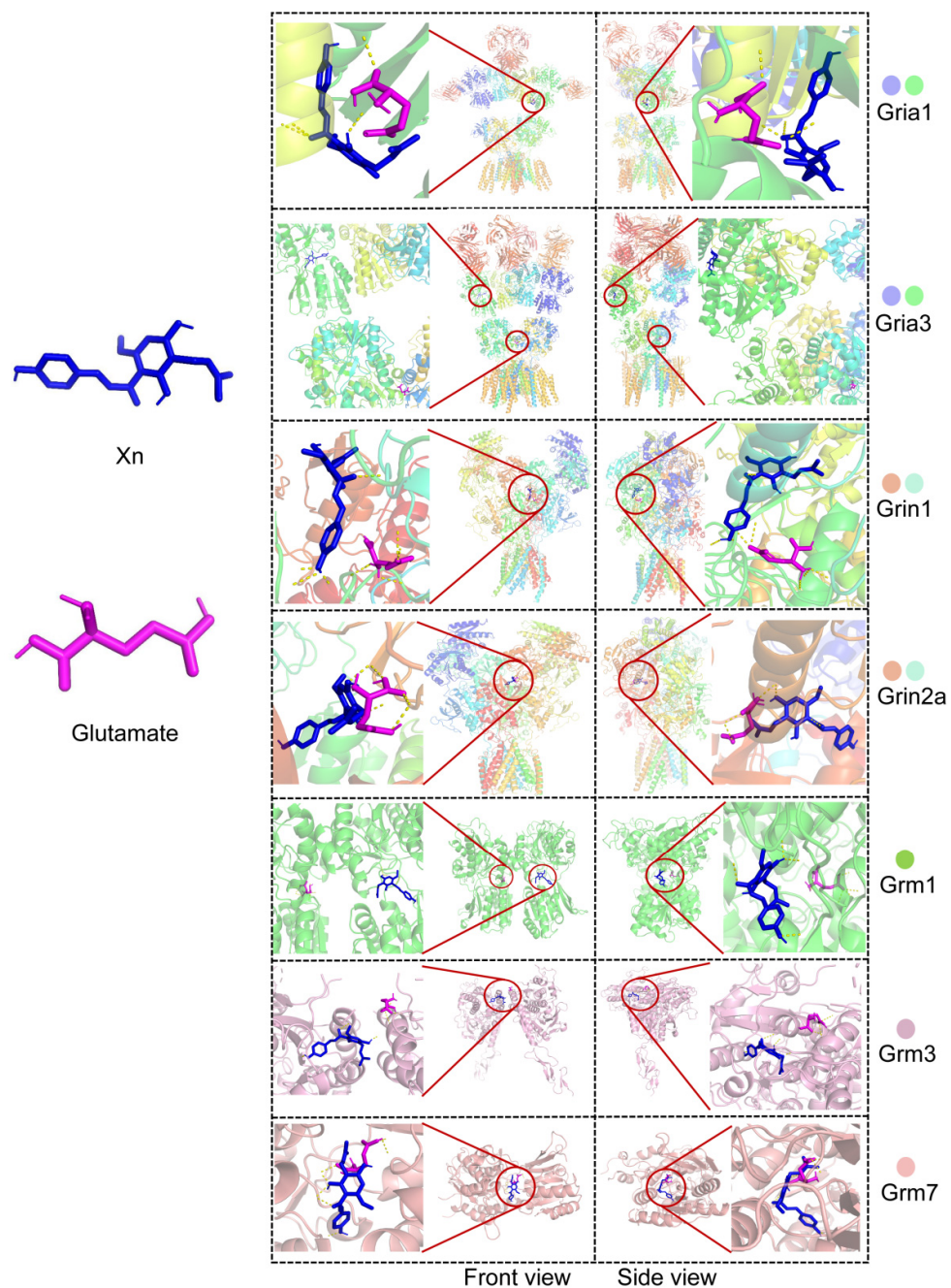


Figure S4. Molecular docking of xanthohumol (Xn) and glutamate with glutamate receptors using Autodock. The glutamate receptors include AMPAR (Gria1 and Gria3), NMDAR (Grin1 and Grin2a), and mGluR (Grm1, Grm3, and Grm7). The three-dimensional structure of Xn (purple) and glutamate (blue) are shown in the stick representation. Hydrogen bonds indicate as dashed lines.

Figure S5

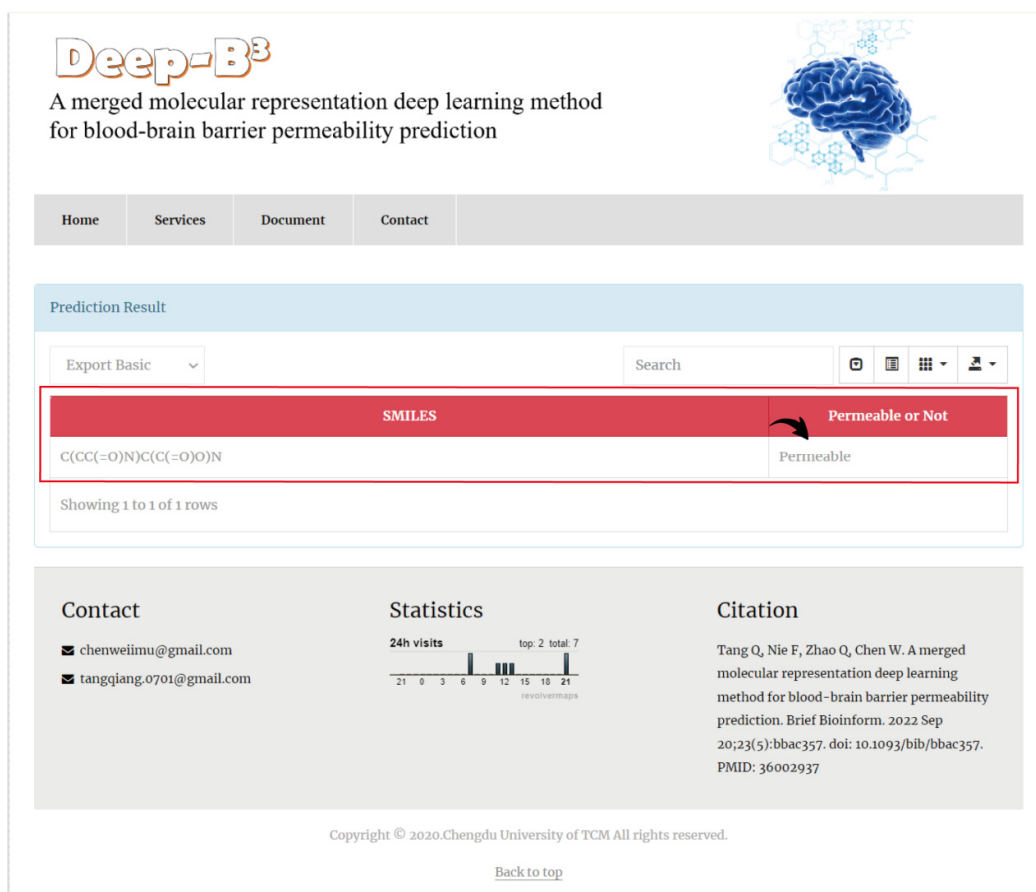


Figure S5. The blood-brain barrier permeability of glutamine predicted by Deep-B³ online web server.